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TRACHEAL AND BRONCHIAL STENOSIS AS CAUSES FOR EMPHYSEMA*

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CLEVELAND

During the past ten years much research has been done on emphysema and asthma and on the chemistry of blood and respired air, but few studies on the mechanism of bronchiolar spasm and emphysema have been published. Some of the most recent work on this subject has been based on the assumption that the time-honored teaching of the causal relation between expiratory dyspnea and emphysema and asthma is unassailable. To me it seems that the prevailing teaching on these subjects needs revision. To learn the mechanism of emphysema and asthma by way of the chemistry of the blood gases and of the respired air seems quite hopeless. When a clear understanding of the mechanism of emphysema and asthma has been attained, we shall be in a much stronger position to interpret our chemical studies of the blood gases and respired air.

BIERMER'S THEORY

The modern interpretation of bronchiolar asthma originated with Biermer, of Zurich,[1] who in 1870 published an exposition of the subject. Biermer referred to Paul Bert as having proved that vagus excitation causes bronchiolar contraction, although it had been suspected, claimed, in fact, by Williams in 1840 at a meeting in Glasgow.[2] Biermer said that the low position of the diaphragm could not be reconciled by his contemporaries to bronchiolar spasm as an explanation for pulmonary emphysema. Bamberger believed phrenic spasm to be the source of acute pulmonary emphysema, and Lehman took the same view.

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* From the Department of Medicine, Western Reserve University, Lakeside Hospital.

* Read before the Meeting of the Association of American Physicians at Atlantic City in May, 1921.

1. Biermer: Innere Medicin, Volkmann's Sammlung klin. Vorträge, No. 3, Leipzig, 1870-1875.

2. Tenth meeting of the Association for the Advancement of Science.

It is with much satisfaction that Biermer quotes the experiments of Paul Bert.[3] Biermer conceived an essential difference to exist between stenosis in the remote branches of the bronchi and stenosis in the trachea. He regarded dyspnea of bronchiolar stenosis as essentially expiratory, because he believed that the active character of the expiration of asthma produced a vicious cycle; an active pressure on the lung compressed the boundaries of the respiratory units, the air cells were subjected to compression, and the air passages connecting them with the larger bronchi were also compressed; that is, the more active the expiratory effort, the greater grew the resistance to exit of air from the respiratory units. On this account the expiratory phase was supposedly much prolonged. Biermer says that the difference between tracheal and bronchiolar stenosis lies in the fact that the former is an inspiratory and the latter an expiratory dyspnea. As an evidence of this point of view, he calls attention to the inspiratory retraction in the supraclavicular, suprasternal and epigastric regions in tracheal stenosis, and contrasts it with the labored expiration of asthma; and he calls attention to the want of evidence of active vigor in the expiratory phase in cases of tracheal stenosis.

NATURE OF ACUTE EMPHYSEMA

By way of introduction to the subject, let it be understood that we are dealing with two phenomena; viz., bronchiolar hypertonus and emphysema of the lungs which consists solely of an increase in the pulmonary residual air. In such cases there is only altered physiologic function and no anatomic disease of the lung.

Bronchiolar spasm is immediately attended with emphysema, diminution of vital capacity, inspiratory and expiratory dyspnea and lessened extensibility and compressibility of the lungs. Thus far, we have no evidence that disturbances in the pulmonary circulation contribute to rigidity of the lungs in acute pulmonary emphysema. The loss in extensibility is due entirely to emphysema and narrowing of the bronchial tree. Although we have no positive evidence for hyperemia of the pulmonary circulation in bronchiolar spasm, there is good negative evidence against its responsibility for rigidity of the lung. That hyperemia can reduce the vital capacity of the lung quite as much as does bronchiolar spasm has often been observed. Both conditions may reduce the vital capacity of the lung to 800 c.c. in persons who normally may have a vital capacity of 4,000 c.c. It is, however, incomprehensible how such an hyperemia could occur without causing great resistance to the work of the right heart and thus causing ectasis of the right ventricle and right auricle. I have never seen any evidence

3. Bert, Paul: The Comparative Physiology of Respiration, 1870.

of enlargement of the right side of the heart in acute bronchiolar spasm. Evidence for it has never been adduced, although in the literature on the subject this assumption commonly appears. The mechanism of bronchiolar spasm, with all its attending attributes, may appear and disappear with such suddenness that it seems inconceivable that the collective phenomena can have any other origin than a neuromuscular performance.

This aspect of acute emphysema is best seen in patients who have periodic bronchiolar spasm from vagus excitation due to mediastinitis. Such a patient came under my observation during an attack.

CASE 1.—The patient was a little girl, 8 years old, who for the last two years had been quite well, according to the grandmother's account, except for asthma, which occurred every few weeks and lasted only half an hour. The last attack of asthma this child had suddenly terminated while I was observing the volume and excursion of her lungs. The lungs filled the pleural sinuses, and the child was employing her utmost effort to breathe during both inspiration and expiration. Each respiratory cycle exhibited her vital capacity, when suddenly in the midst of a single respiration, the lower border of the lung was seen to ascend 4 cm., and with this rapid disappearance of emphysema there was a complete return of respiratory comfort.

It can truthfully be said that this child began a respiratory cycle with emphysema, lessened vital capacity, inspiratory and expiratory dyspnea, lessened extensibility and compressibility of her lungs, and ended the cycle with respiratory euphoria. It is inconceivable that such a rapid disappearance of all these symptoms could be produced by any other than a neuromuscular phenomenon. The recovery was too rapid to include vasomotor phenomena, with consequent changes of blood distribution, as among the causes of the symptom complex. There is, therefore, very good reason for excluding all proposed possibilities except bronchiolar spasm as the cause of acute emphysema. But we find the theory of the mechanism by which bronchiolar spasm is supposed to produce emphysema and its attendant symptoms does not withstand clinical and experimental criticism.

TRACHEAL STENOSIS

Biermer's theory teaches that bronchiolar spasm is attended with an expiratory effort, which produces a vicious cycle by compressing the bronchiolar exits from the respiratory units. If this be true, a resistance anywhere in the tracheobronchial tree which is sufficient to demand expiratory compression of the lung should lessen the volume flow toward the latter part of expiration, as the intrapleural pressure rises, and result in emphysema and prolongation of the expiratory phase. If a strong muscular effort is needed to accomplish expiration against tracheal resistance, the same mechanism of expiratory stenosis should be operative that Biermer's theory teaches for bronchiolar

hypertonus. If active compression of the distended lung by the employment of expiratory muscles produces a vicious cycle of expiratory stenosis when there is bronchiolar hypertonus, then there is no reason apparent why the same process should not operate when the resistance to expiration is located in the trachea.

According to the prevailing theory, in the presence of great resistance to expiration located in the trachea there should be pulmonary emphysema and a prolongation of expiration proportionately greater than the prolongation of inspiration, but the clinician rarely has an opportunity to investigate this theory. By the time the patient with tracheal stenosis comes under observation, there is nearly always a complicating tracheobronchitis with infection of the bronchial tree. What the clinician usually sees is tracheobronchitis complicating tracheal stenosis. Under these conditions the patient may have much moisture in the air spaces and there may be a complicating bronchiolar hypertonus, so that it is quite impossible to separate the effects of the two lesions so far as the clinical manifestations are concerned. I have seen patients with laryngeal diphtheria who had pulmonary emphysema, but these same patients had tracheobronchitis as well as the laryngeal stenosis, so that one would not be justified in saying the patient's emphysema was the result of laryngeal stenosis. It could just as well originate from the bronchitis. However, during the influenza epidemic of 1919 I had an opportunity to see a case of uncomplicated tracheal stenosis.

Case 2.—A well-grown girl, about 17 years of age, had been ill for three days with epidemic influenza. There had been a very considerable amount of tracheitis from the start. There was some dulness at the base of the right lung, but there was no elevation in the pitch of the respiratory sounds and the patient was not cyanotic. Until the evening of the third day no alarming symptoms had developed, but about 10 o'clock on the night of the third day of her illness, she became quite dyspneic. At 12 o'clock she had severe stenosis of her trachea, about half way between the glottis and the bifurcation, which was due to edema of the tracheal mucosa. With the laryngoscope the livid swollen mucosa and the very narrow slit in the lumen of the trachea could very plainly be seen. This patient was doing her utmost to breathe. She employed a violent effort of all the inspiratory muscles during inspiration, and likewise employed violent contraction of all her abdominal muscles and intercostals during expiration. There was no undue prolongation of the expiratory phase and there was no evidence of increase in the volume of the lung. The patient died about two hours later from respiratory exhaustion due to stenosis of the trachea, but there was not the slightest evidence of emphysema.

It might be objected that in this particular patient the equality of resistance to inspiration and expiration was the reason why she did not have emphysema, but later we had the opportunity of seeing a patient who had an expiratory resistance in the trachea which greatly

exceeded the resistance to inspiration, and there was no pulmonary emphysema.

CASE 3.—A man having an aneurysm of the ascending arch of the aorta, which compressed the trachea at the bifurcation, was brought into the hospital in one of his attacks. It was quite apparent that the patient accomplished his inspiratory act with comparatively little effort. There was some resistance to inspiration, but the inspiratory dyspnea was not excessive, and it was quite plainly apparent that there was less dyspnea during the latter part of inspiration than at the beginning of the phase. In other words, as the man lifted his thoracic cage, the compression of the trachea lessened, but during expiration it was equally apparent that the resistance to the exit of air increased as the expiratory phase progressed. The expiratory phase was greatly prolonged and was attended with violent contractions of the abdominal and intercostal muscles. The man was employing his utmost effort to expel air from his lung during the latter part of the expiratory phase. This was due to the fact that, as the expiratory phase progressed and the thoracic cage was driven downward on his aneurysm, the stenosis of the trachea increased, so that the stronger his expiratory effort, the more ineffectual it became.

This was an instance of expiratory dyspnea, of a high degree, located in the trachea, but the volume of the patient's lung was not increased during the attacks. We had an opportunity to see him in several of these experiences, which were very distressing and seemed to threaten the patient's life, but the volume of the lung during the paroxysms (which lasted several hours) did not increase. This patient's expiratory dyspnea was just about as severe as a patient could endure and yet survive.

I could not conceive of a more successfully designed experiment to prove the fallacy of Biermer's theory of expiratory stenosis than this patient exhibited in his several paroxysms. It was this experience that suggested animal experiments to see what effect obstruction to inspiration and expiration, respectively, may have on the volume of an animal's lung when the seat of the obstruction is in the trachea.

EXPERIMENTAL TRACHEAL STENOSIS

A wooden box, 31x10x9 inches, was constructed with a shelving top, which enabled us to seal the open top of the box with a glass plate laid in petrolatum. With an animal confined in this box, which served as a plethysmograph, we could connect the cannula inserted in the animal's trachea with the exterior through a tube, which was passed through a rubber cork placed in a hole in the side of the box. Through a Meltzer cannula inserted in the pleural cavity, we were able to register the intrapleural pressure by means of a tambour, which was connected with the tube leading from the Meltzer cannula through a cork in the side of the box. By the same means we connected a cannula in the dog's jugular vein with the exterior. The animal could breathe the room air, or any other atmosphere, and by connecting the cavity of the box with the spirometer of a Benedict apparatus, we could record the respiratory excursions and detect any modifications in the volume flow of air during inspiration and expiration quite as accurately

as when the tracheal cannula was connected with the spirometer. In fact, the plethysmographic excursions of the spirometer were perfect reproductions of the excursions of the spirometer when the animal breathed directly into the reservoir. Each millimeter of elevation of the reservoir represented a volume of 22 c.c. When the spirometer was used for recording the plethysmographic excursions, the tubes leading to the canister were cut off, so that there was simply a to and fro movement of air between the Benedict reservoir and the air of the box which contained the dog. We could thus accurately measure not only the character of the inspiratory and expiratory excursion and its exact volume, but we could accurately measure any variation in the minimum volume of the animal's lung.

The tracheal cannula connected through the side of the box with room air, and on the end of this tube one could fix various sorts of appliance; for instance, a screw clamp was used on a piece of rubber tubing which was attached to the tube connected with the tracheal cannula, and in this way we could give the animal any degree of stenosis to inspiration and expiration alike. By a Y tube fixed to the tracheal cannula and clapper valves, we could give the animal any degree of stenosis to expiration only and leave inspiration unobstructed; or we could do the reverse and give the animal any degree of resistance to inspiration and leave expiration unobstructed.

The animals employed varied greatly in size, the largest weighing seventeen kilos. Many times there was no change in the volume of the animal, and we never got an increase in volume above 66 c.c. when tracheal stenosis to inspiration or expiration was employed.

The dog was given chlorbutanol (dissolved in oil) in the peritoneal cavity, and morphin was given hypodermically. We attempted to use the minimum dose of chlorbutanol and morphin, but it was necessary to keep the animal at rest while fixed within the plethysmograph.

One of the greatest difficulties was to procure active expiration in an anesthetized animal. Obstructing respiration and permitting the carbon dioxid to accumulate within the body, or having the animal rebreathe into a bag containing 80 per cent. oxygen and 20 per cent. carbon dioxid, would not secure active expiration. Resistance to inspiration very readily activated the muscles to increased effort, but when tracings of intrapleural pressure were made, we found that resistance to both inspiration and expiration was not sufficient to induce active expiratory effort. *It was only after a high degree of hyperpnea was induced by having the dog rebreathe an atmosphere of oxygen and carbon dioxid that we could induce an active respiratory effort by shunting in a resistance to expiration.* This is mentioned because, in the literature on the subject of respiratory excursions, many writers

have assumed that, because respiration had been suspended or the animal was compelled to breathe an atmosphere with a high concentration of carbon dioxid, therefore the hyperpnea was accompanied by an active expiratory effort. *It was found after many trials that, to procure an active expiratory effort so that during expiration the pressure in the pleural cavity would be raised above barometric pressure, it was necessary first to induce a very active hyperpnea and then during the period of hyperpnea to shunt in the expiratory resistance.* Under these circumstances the threshold for active respiration was passed and a positive pressure in the pleural cavity was obtained above that of barometric pressure.

Experiment 1.—Figure 1, line A, should be read from right to left. From 1 to 2, we see four normal respiratory excursions recorded by the plethysmograph. Line A is the base line and marks the minimum volume of the dog at the end of expiration. At 2 the animal was made to rebreathe into a bag containing 80 per cent. oxygen and 20 per cent. carbon dioxid. Each 5 mm.

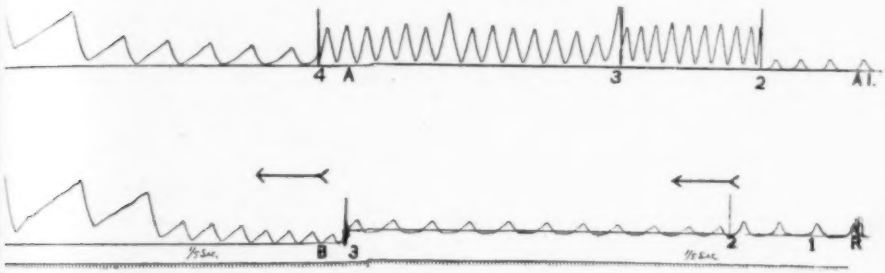

Fig. 1.—Experiment 1.

in the time marker represents 1 second, so that 1 mm. equals 1/5 second. As can be seen by the tracing, inspiration and expiration were of about the same duration; and while the animal was breathing room air, 1 second was occupied to complete the respiratory cycle, and the animal breathed about 70 c. c. with each respiration.

When the dog began rebreathing the high concentration of carbon dioxid, the time occupied in the respiratory cycle was 1 second; the rate was very much increased, and the volume of each excursion was 286 c. c. From 2 to 4 the animal was rebreathing the carbon dioxid without resistance to either inspiration or expiration, and then at 4 a valve was inserted in the end of the tube connecting with the tracheal cannula, which gave the animal a perfectly free inspiratory movement but very greatly restricted the expiration. The volume flow through the expiratory valve under a pressure of 80 mm. of water was 1,200 c. c. per minute. Inspiration occupied 3/5 second, but the duration of the respiratory cycle was 13/5 seconds; so that the proportional duration of inspiration to expiration was 3 to 10. The volume of excursion as the animal began breathing at 4 was 132 c. c. As will be seen by the tracing, in the first five respiratory cycles there was a gradual rise in the volume of each respiration, and then it is seen that the stimulus to respiration due to the carbon dioxid accumulation produced a large excursion of 400 c. c. The duration of inspiration in this cycle was 5/5 second, but the duration of expiration was

25/5 seconds, and the volume of the dog at the end of expiration had increased 154 c.c. As this tracing was continued, the respiratory excursion became more rapid, and the minimum volume of the dog at the end of expiration had increased about 250 c.c. above the original volume. So that we can say that this experiment shows that, when an expiratory obstruction is shunted into the trachea in an animal with great hyperpnea, the residual air in the lung is very greatly increased. When, however, one carried out the experiment in reverse order, and as shown in line B, the dog breathed room air from 1 to 2 and then at 2 the expiratory valve was placed in the end of the tracheal cannula, so long as the dog was breathing room air and there was no occasion for hyperpnea the volume of the dog was unchanged. At 3, however, the animal continued to breathe with an expiratory resistance, when he was connected with a bag containing 80 per cent. oxygen and 20 per cent. carbon dioxid. By the end of the seventh respiratory cycle, there was a large inspiration of 352 c.c., and the same increase in the residual air of the dog became apparent as in line A at 4. As seen in one of the larger excursions, the duration of the respiratory cycle was 30/5 seconds, inspiration occupying only 4/5 second, and expiration 26/5 seconds.

Although in this experiment the intrapleural pressure was not measured (because I wished to leave the thorax intact), I think we are justified in assuming from repeated trials in former experiments that with this resistance to expiration added to the great hyperpnea from breathing carbon dioxid, the animal was actually employing effort during the expiratory phase. This experiment showed that the only way in which tracheal resistance will increase the residual air in the lung is in conjunction with increase in the volume of respiratory excursion. In this animal the volume of excursion was increased from 70 c.c. up to 300 c.c. by rebreathing carbon dioxid, and the rate of respiration was increased from 36 to 52 per minute.

The phenomena described in this experiment do not occur in bronchiolar spasm. A patient who has a violent spasm can supply his oxygen needs perfectly well by a 25 per cent. increase in the oxygen consumption and the minute volume of air. I have repeatedly taken Benedict tracings on patients during periods of bronchiolar hypertonus, and during severe spasm we have found both the minute volume of respired air and the consumption of oxygen just about 25 per cent. greater than in the interims of respiratory comfort. The increase in each is imposed on the patient by the additional work required to ventilate his lungs. This introduces another essential consideration of asthmatic breathing—that is, that the residual air in the lung is greatly increased, although the increase in the minute volume of ventilating air is slight. In bronchiolar hypertonus without hyperpnea, emphysema is produced, but in tracheal expiratory dyspnea, emphysema is obtained only in the presence of hyperpnea, which must be superadded to the expiratory resistance.

The clinical and experimental evidences reveal an essential difference between the results of bronchiolar hypertonus and stenosis of the

trachea. When the tracheal resistance to inspiration and expiration are equal, there is no increase of residual air in the lung. In the absence of hyperpnea, resistance to expiration in excess of that to inspiration will not increase the volume of the lung.

BRONCHIAL HYPERTONUS, REGIONAL AND OF ANY DEGREE

The Biermer doctrine of the mechanism of emphysema in bronchiolar hypertonus demands an active expiratory compression of the lungs. But moderate bronchiolar hypertonus produces emphysema when there is no active effort attending expiration. Expiration may remain a passive procedure and still be attended with emphysema. When the conception of emphysema from bronchiolar hypertonus first appealed to me as a problem for investigation, I was in the habit of thinking of bronchiolar hypertonus as a neuromuscular performance that belonged to the all-or-nothing law, and also that it was equally distributed throughout the bronchial tree. Neither of these conceptions is true. Neuromuscular reaction in the bronchial tree may, like vasomotor reaction in the arterial bed, be of any degree and may also be universal or regional. A patient may have a moderate bronchiolar hypertonus attended with demonstrable emphysema of the lung but without sufficient bronchiolar resistance to call out an active expiratory effort on the part of the patient. A few clinical cases will suffice to prove these statements.

REPORT OF CASES

Case 4.—A man, 60 years of age, who had suffered from bronchitis and occasional asthmatic paroxysms for a period of five years, had a very moderate pulmonary emphysema, which at the borders of the lungs was sufficient to fill the pleural sinuses, but the total lung volume was not increased so that the diaphragm was sufficiently flattened to change the normal direction in the movement of the costal margins during inspiration. According to this man's account, his breathing was never completely shunted out of the field of consciousness. He was always aware of a certain degree of respiratory discomfort, but from physical examination and roentgenograms of the lung one could not determine how much of his discomfort should be ascribed to atrophic emphysema and how much to bronchiolar hypertonus. When he was given a subcutaneous dose of 20 minims 1:1000 epinephrin, the vital capacity of his lung increased from 2,000 to 2,500 c. c., and he then said that for the first time in a year he experienced complete respiratory euphoria. Before the epinephrin was given, this patient did not have an active expiratory phase, although he had a certain degree of bronchiolar hypertonus with consequent emphysema, as shown by the respiratory comfort and increase in vital capacity directly after adrenalin was given. His respiratory discomfort had evidently consisted in an increased effort during inspiration. Of this effort he was conscious, but his pulmonary ventilation was still adequate to preserve the passive character of his expiration. His expiration was prolonged, but the moderate dyspnea permitted the expiratory prolongation.

Case 5.—Another patient was a young, vigorous man, 25 years of age, who complained of respiratory discomfort, which had lasted for twenty-four hours. It was quite apparent that the man had labored breathing, but examin-

ation revealed that his labor was all on the inspiratory side; there was no effort during the expiratory phase, the abdominal muscles being perfectly relaxed. The costal margins moved outward throughout their entire extent during inspiration. There was sufficient emphysema, however, at the borders of the lungs so that they filled the pleural sinuses as far as the eighth interspace in the nipple line and the eleventh rib in the axillary line.

The patient showed very marked relief from the administration of adrenalin. Before the administration his vital capacity was 3,350 c. c. when seated, and 2,951 c. c. when recumbent. Ten minutes after he had been given 20 minims 1:1000 epinephrin hypodermically, his vital capacity when seated was 3,478 c. c., and 3,415 c. c. when recumbent. His respiratory rate both before and after epinephrin varied between 22 and 24. Before he had his epinephrin when the respiration was traced on a rotating drum, which was running at the rate of 5 mm. per second, in a respiratory cycle during which he breathed 528 c. c. the duration of the entire cycle was 22/5 seconds. The inspiratory phase was 10/5 seconds, and the expiratory phase 12/5 seconds. After he had epinephrin, in a respiratory cycle in which he breathed 726 c. c., the duration of the cycle was 19/5 seconds, the inspiratory phase occupying 8/5 seconds and the expiratory 11/5 seconds. So it is quite apparent that both before and after epinephrin there was no active expiratory phase.

Although the test showed only a comparatively slight increase in his vital capacity after epinephrin, the lung passively expelled 726 c. c. in 11/5 seconds, whereas prior to the administration of epinephrin the lungs passively expelled 528 c. c. in 12/5 seconds. The rigidity of the lung was considerably less after epinephrin than before. The inspiratory effort had been quite apparent to inspection, and the inspiratory and expiratory phases were accompanied by a number of coarse, moist and sibilant râles, all of which disappeared after epinephrin took effect. The only direct evidence we procured to show diminution in volume of the lung after epinephrin was that, while the lower border of the lung had been at the eleventh rib in the axillary line before epinephrin, it was afterward at the ninth interspace. In the midclavicular line, it was at the eighth interspace both before and after epinephrin was given. However, it was quite apparent to the observer that the epinephrin relieved the man of a very considerable degree of respiratory discomfort.

These patients with demonstrable bronchiolar hypertonus had a very considerable degree of respiratory discomfort (that is, inspiratory), but the vital capacities of the lungs were very little modified by the hypertonus. According to the size and conformation of the second man's thorax, he should have had a vital capacity of at least 5,000 c.c. Without the use of epinephrin it would have been impossible to show that bronchiolar hypertonus played a part in his respiratory discomfort.

The following cases showed regional hypertonus:

Case 6.—This patient had had a moderate general bronchiolar hypertonus, but on one occasion it was only regional. The resident physician found one night that his right thorax was comparatively immobilized, with no respiratory excursion perceptible in the arches of the right ribs. The whole right thorax was distinctly larger than the left. There was a distinct asymmetry, which had not been visible on other occasions. During the inspiratory phase, the entire right costal border was drawn strongly toward the median line, but the left moved vigorously in a lateral direction, and the respiratory excursion of the entire left thorax plainly exhibited an exaggerated excursion. The arches of the left ribs moved in their normal bucket handle manner much more actively than during interims of comfort. It was plainly apparent that

the right thorax was enlarged, that the right diaphragm was flattened, and that there was very slight respiratory excursion on that side. It was also apparent that there was a compensatory increase in the respiratory excursion of the left side, the minute volume of air in the left lung being equal to that of both lungs in the interims between attacks. In other words, the man had an acute unilateral bronchiolar spasm. This was also confirmed by auscultation. Over the entire right side there was an abundance of squeaking and moist râles during inspiration and expiration, but the left lung was free. The respiratory sounds were only faintly audible over the right side, whereas they were distinctly heard over the left, where the excursion was magnified. This patient was probably breathing a little larger minute volume of air than he employed during his interims of comfort, but the greater part of the pulmonary ventilation was accomplished with the left lung.

Twenty minims of 1:1000 epinephrin were given this patient hypodermically, and within a very few minutes he recovered his normal thoracic excursion. The two sides were again symmetrical, with symmetrical outward movement of both costal margins during inspiration. Most of the râles of the right side disappeared. The patient was perfectly comfortable, and so far as physical examination enabled us to determine, he was again ventilating both lungs equally.

CASE 7.—This patient had severe bronchitis and atrophic emphysema, and he had been studied during very many asthmatic paroxysms. On one occasion, however, he complained of discomfort when the auscultatory evidence of asthma was limited to the lower lobe of the right lung. The right costal border was drawn toward the median line during inspiration, whereas the left costal margin moved in an outward direction. After the hypodermic injection of epinephrin, the patient's respiratory comfort was restored within a very few minutes. The auscultatory signs of asthma disappeared from the lower lobe of the right lung, and the right costal border resumed its outward inspiratory excursion, which was quite symmetrical with that of the left side. So far as physical examination enabled us to determine, this patient had a regional bronchiolar spasm attended with emphysema restricted to the lower lobe of the right lung.

CASE 8.—On another occasion we had a patient suffering from chronic bronchitis and emphysema who had an attack of asthma in which all the evidence of asthma was limited to the two upper lobes. There was no evidence of flattening of the diaphragm, but the auscultatory signs of asthma, though very pronounced in the upper lobes, were entirely wanting over the two lower lobes.

It does not seem possible that a patient could produce the expiratory vicious cycle which supposedly occurs in asthma and confine the exhibition of compression of the bronchioles in one instance (Case 6) to the entire right lung, in another instance (Case 8) to the two upper lobes, and still in a third instance to the lower right lobe only (Case 7). Such cases alone offer sufficient evidence to disprove the need of an active expiratory phase to produce emphysema during an asthmatic attack.

DURATION OF EXPIRATION

To return to our cases of general bronchiolar hypertonus (Cases 4 and 5), attended with moderate emphysema and prolongation of the expiratory phase. The expiratory phase in all the patients with moderate hypertonus was longer than the inspiratory phase simply because the resistance to expiration was not sufficient to demand an active

compression of the lungs. To cause a transition from passive to active expiration, the obstruction to the passage of air must be so great that the time required for passive expiration exceeds the tolerance of the patient's respiratory needs. So long as bronchiolar hypertonus will allow a passive expiratory phase, the patient will instinctively refrain from active compression of the lungs by simultaneous action of the abdominal and intercostal muscles. The active expiration demanded by stenosis of the bronchial tree is very exhausting. Resistance to inspiration requires only an increase in the force of activation of the muscles normally employed; but resistance to expiration not only requisitions muscles which are not normally employed (which in itself is very exhausting), but produces an unfavorable effect on the hydraulics of the blood circulation in the thorax. In animal experiments the extremity of the measures which are required—namely, hyperpnea plus obstruction—before the animal can be induced to raise the expiratory pressure above the barometric pressure, plainly illustrates the height of this threshold for active expiration. These facts clearly explain why a patient with moderate bronchiolar hypertonus will have the duration of the expiratory phase shortened after the administration of adrenalin. Adrenalin given to such a patient will also have the effect of diminishing the residual air in the lung and will increase the pulmonary vital capacity.

How is the expiratory phase affected in a patient who has a bronchiolar hypertonus so severe that an active expiration is demanded? Figure 2 is a tracing taken with the Benedict apparatus during an attack of bronchiolar hypertonus. On line B is a tracing after the hypertonus was relieved by 20 minims of 1:1,000 epinephrin given hypodermically. When the tracing in line A was made, the patient was in great distress. The volume of each lung was so increased that the flattened diaphragm drew the costal borders toward the median line during inspiration, and the expiratory phase was accomplished by violent contraction of the abdominal muscles. These conditions are exactly such (according to Biermer's doctrine) as to create a vicious cycle of dyspnea, and should have caused a prolongation of the expiratory phase with a lessened volume flow of air toward the latter part of expiration. But the tracing reveals the opposite of that expected under the Biermer theory.

Experiment 2.—This tracing was taken on a drum with the speed of 1 mm. per second. The respiratory rate before adrenalin was given was 16 per minute. The line of the inspiratory phase on the upstroke is straight, and the line of the expiratory phase is equally straight. There is no lagging or horizontal drag as must occur in such a tracing should the volume flow lessen toward the end of expiration. The transition from inspiration to expiration and that from expiration to inspiration show very sharp peaks. The tracing indicates just what we were able to observe in the patient at the time. He

was employing his utmost muscular strength during all of inspiration and expiration, and the volume flow of air was uniform throughout the entire respiratory cycle.

On line B we see the effect of the respiratory cycle after the bronchiolar spasm had been relieved by the hypodermic injection of 20 minims of 1:1000 epinephrin. The respiratory rate was then 14 per minute. The inspiration on the upstroke is not quite so nearly vertical as before the epinephrin was given, and we can see toward the end of the expiratory phase a distinct slope

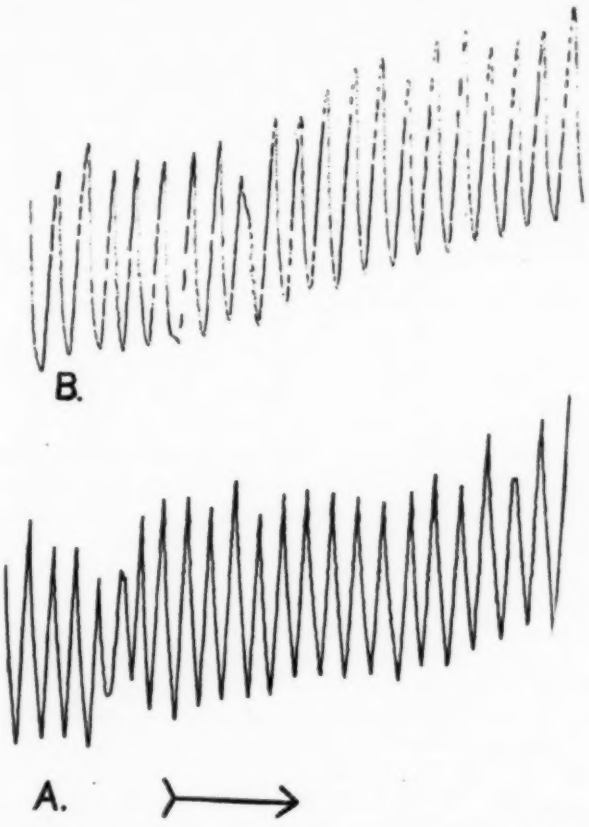

Fig. 2.—Tracing taken with Benedict apparatus during attack of bronchiolar hypertonus.

to the right, which means the volume flow toward the end of the expiratory phase was distinctly lessened. During the time the tracing in line B was taken, the patient had distinct inspiratory widening of his subcostal angle. Expiration was not attended with contraction of the abdominal muscles. In fact, he was breathing with perfect comfort. The difference was that before he had his epinephrin he was able to attain his required pulmonary ventilation at the

expense of great muscular effort during both inspiration and expiration. The expiratory labor was very exhausting, although the actual increase in oxygen consumption was only 25 per cent. in excess of what he employed during tranquil breathing at rest. The source of exhaustion is not in this instance measurable by the increased consumption of oxygen but by the employment of an unusual kind of expiratory effort.

With the Biermer doctrine of expiratory dyspnea in mind, one would be disposed to say that line B was traced before epinephrin was given, and that line A was traced after the bronchiolar hypertonus had been relieved. This tracing shows a longer expiratory phase after bronchiolar hypertonus was relieved simply because the patient had a passive expiratory phase and his respiratory needs did not demand compression of the lungs during expiration. Tracing A not only shows that the patient employed a positive pressure in his pleural cavity during the expiratory phase, but it shows that the minute volume flow of air during the latter part of the expiratory phase was more constant than when he was breathing with a passive expiration.

These experiments not only prove the fallacy of the doctrine of expiratory dyspnea in asthma, but they also show the error of employing the prolongation of the expiratory phase as an index of the severity of bronchiolar spasm.

EXPIRATORY COMPRESSION STENOSIS OF THE BRONCHI

The question of expiratory dyspnea arising from compression stenosis in the bronchial tubes remains for experimental consideration. If bronchiolar spasm is severe enough to require active compression of the lungs in expiration, there are two forces employed to expel air from the lungs: one the positive intrapleural pressure due to activation of the abdominal and intercostal muscles, and the other the retractile property of the visceral pleura and the elastic tissue within the lungs. If active compression of the lungs produces stenosis of the small branches of the bronchi in the presence of bronchiolar spasm, why should it not do the same in the absence of bronchiolar hypertonus? It seems reasonable to suppose that in the absence of hypertonus the bronchi would be more compressible than when they are hypertonic. If hyperpnea is induced in an animal by suffocation or by breathing a high concentration of carbon dioxid, and then tracheal stenosis is added to the respiratory burden so that compression of the lung is required to accomplish expiration, then under such experimental conditions we can measure the volume flow of air from the trachea and also the pressure on the proximal side of the tracheal stenosis, and synchronously with these air pressure and air volume flow measurements we can also trace the expiratory pressure in the pleural cavity. In such an experiment the expiratory forces are pitted against the tracheal resistance, with a certain volume flow as a result. Should an expiratory resistance to the outflow of air intervene between the air cells and the tracheal obstruction, then the volume flow of air should lessen toward the latter part of expiration, and the sum of the expulsive forces should exceed the air

pressure maintained in the trachea on the proximal side of the stenosis. The expulsive forces are of course the pressure within the pleural cavity and the retractile power of the lung.

Experiment 3.—A dog weighing 16 kilos was anesthetized with chlorbutanol and morphin. Tracheotomy was then done, and two cannulas introduced, one into the trachea and one into the right pleural cavity, after which the dog was placed in the plethysmograph. The cavity of the box was connected with the reservoir of a Benedict apparatus and the passages to the canister clamped so that there was a free movement to and fro between the confined air in the box which contained the dog and the air in the registering reservoir. The volume flow of air during each respiratory cycle could thus be accurately traced on a revolving drum, which had a speed of 5 mm. per second (Fig. 3, line *Pleth*). The time is marked in fifths of seconds. By a tube which passed through a cork in the side of the box, the Meltzer cannula in the pleural cavity was connected with a calibrated tambour, which traced the pressure in the pleural cavity for each respiratory cycle (see line *Pleura*). A T tube was inserted in the tube to the pleural tambour, by means of which we could

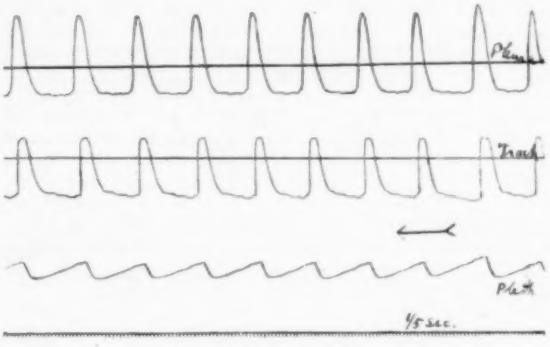

Fig. 3.—Experiment 3.

introduce into or remove from the pleural cavity any desired quantity of air. The tracheal cannula was connected with a tube which passed through a cork in the side of the box, and to the end of this tube was fitted a Y tube, the afferent limb of which was fitted with a clapper valve, while the efferent limb had its lumen modified at will by means of a screw clamp.

On the proximal side of this Y tube which terminated the tracheal cannula, was introduced a T tube, which connected with a calibrated tambour by means of which could be traced the air pressure on the proximal side of the expiratory obstruction. The writing styles for the plethysmograph and tracheal and pleural tambours were then perfectly aligned, so that a vertical line drawn anywhere would enable us to make accurate comparison of the three tracings in any phase of the respiratory cycle. In both the pleural and tracheal pressure tracings, the horizontal line traces the line of barometric pressure. The time tracing is in fifths of seconds. In all three tracings the upstroke records inspiration and the down stroke expiration, and they are read from right to left. They were made after 1,050 c. c. of air had been injected into the right pleural cavity. This injection was to prevent any error in getting the exact intrapleural pressure and also to procure any evidence of expiratory bronchiolar compression which the partial collapse of the lungs might offer.

Preceding this part of the tracing the screw clamp on the efferent limb of the tracheal Y tube was screwed down to procure the maximum resistance against which the animal would breathe. Respiration was arrested by complete obstruction of the tracheal cannula for one minute, and the drum was started as the complete obstruction of the tracheal cannula was released. The afferent clapper valve offered slight resistance to inspiration, as shown by the rise of the pressure curve of the tracheal tambour above the line of barometric pressure (minus pressure). The combination of hyperpnea with resistance in the efferent limb of the Y tube to the tracheal cannula induced an active expiratory phase, as shown by the rise above barometric pressure in the pleural cavity (below the pleural barometric line).

The plethysmographic tracing shows each respiratory cycle to have a duration of 17/5 seconds, the inspiratory phase occupying 3/5 seconds, and the expiratory 14/5 seconds. The volume of each respiration was 110 c. c. The volume flow tracing of expiration is straight; there is no drag to the left as there would be if the flow diminished toward the latter part of the expiratory phase.

When the positive pressure below the barometric lines of pressure for the trachea and pleura are measured, the pleural pressure of 9 mm. registered by the tambour style is found to equal 70 mm. of water, and the 12 mm. registered by the tracheal tambour style at the same time equals 100 mm. of water. But to the air pressure within the pleural cavity must be added the elastic contracile force of the lung. In this dog the intrapleural pressure measurements were taken when the animal was breathing freely without obstruction, and the pleural cavity was free of all but 50 c. c. of air. The intrapleural tracings then showed a pressure below the barometric pressure of 70 mm. of water at the height of inspiration, and 30 mm. of water at the end of expiration. If these 30 mm. are added to the maximum intrapleural pressure attained during the expiratory phase, we find the sum of the two factors (70 + 30) exactly equals the positive pressure measured on the proximal side of the screw clamp on the efferent limb of the tracheal cannula, and furthermore the minute flow is constant during the entire expiration. *We are justified in saying that under these experimental conditions there can be no resistance to the exit of air intervening between the air cells and the point of obstruction on the efferent limb of the tracheal cannula.*

Repeatedly hyperpnea was produced by having the animal rebreathe into a bag containing 80 per cent. oxygen and 20 per cent. carbon dioxid, and then resistance was applied in the tracheal path. By these means we were able to develop a high pressure in the pleural cavity during expiration, and the same results were always procured. After each experiment the tambours were calibrated for pressures above and below barometric pressure. In the dog the mediastinal reflections of the pleura are so mobile and offer so little resistance that a positive pressure obtained on one side of the thorax by producing an active expiration will be the same on both sides.

In measuring the volume of an animal under these experimental conditions, great care must be observed to guard against leakage of air into the pleural cavity. If air enters, the volumetric measurements of the plethysmograph will record an increase in volume of the thorax which apparently varies with the resiliency of the animal's thoracic cage. In one experiment, 100 c.c. air injected into the right pleural cavity increased the volume of the dog 120 c.c., and when 500 c.c were

injected, the dog increased 360 c.c. in volume. If this source of error is not considered, the increase in volume may be interpreted as an increase of the residual air in the lungs.

Thus far the studies of tracheal obstruction show several results that are of interest in relation to the study of resistance to the respiratory passage of air:

1. If the obstruction is the same during inspiration and expiration, there will be no increase of residual air, although hyperpnea is demanded for breathing an atmosphere of 80 per cent. oxygen and 20 per cent. carbon dioxid. When there is no hyperpnea, equal resistance to inspiration and expiration fails to produce emphysema.

2. When there is no hyperpnea, equal resistance to inspiration and expiration fails to produce emphysema.

3. In an animal under chlorbutanol anesthesia, the threshold for active expiration is very high and is passed only when hyperpnea is added to tracheal resistance.

4. Expiratory resistance with unobstructed inspiration will not cause emphysema unless the resistance occurs in company with hyperpnea.

5. When active expiration is induced by the combination of hyperpnea with tracheal expiratory resistance, there is no intervening resistance to the exit of air from the lungs that can be located in the bronchial tree, as Biermer's theory assumes there should be to produce emphysema.

These experimental results are quite consistent with the previously described observations on a patient who suffered from severe stenosis of the trachea (Case 3), which caused equal resistance to inspiration and expiration; and they are also consistent with the observations made on the patient who had severe expiratory with moderate inspiratory resistance without the development of emphysema (Case 4)—although the expiratory phase in both patients was accomplished with the utmost prolonged muscular effort of which the patients were capable.

Acute emphysema was procured by animal experiment only when the hyperpnea was combined with expiratory dyspnea in the absence of inspiratory dyspnea. On the other hand, we have shown that emphysema with bronchiolar hypertonus occurs in man when there is no further cause of hyperpnea than a slight effort during inspiration, and when expiratory dyspnea is so moderate that an active expiration is not required and expiration remains a passive procedure.

EXPERIMENTAL BRONCHIAL HYPERTONUS FROM HISTAMIN

We should, then, expect to find emphysema in dogs accompanying the bronchiolar hypertonus that follows intravenous injection of his-

tamin. With this in mind, twelve experiments were performed which were designed to show modifications in the volume of the lung of a dog during the period of bronchiolar hypertonus. The histamin was administered through a cannula, which was previously fixed in the internal jugular vein; and a tube from the cannula led through a cork in the side of the box, so that we could give histamin without disturbing the plethysmographic tracings of respiration. I was never able to find an increase of lung volume above 60 c. c. during the period in which the effect of histamin was apparent, and that was in a dog weighing 16 kilos. This increase in size is practically negligible so far as a consideration of increase in the residual air of the lung is concerned, for such a moderate increase might occur under a variety of disturbances in the cardiorespiratory function.

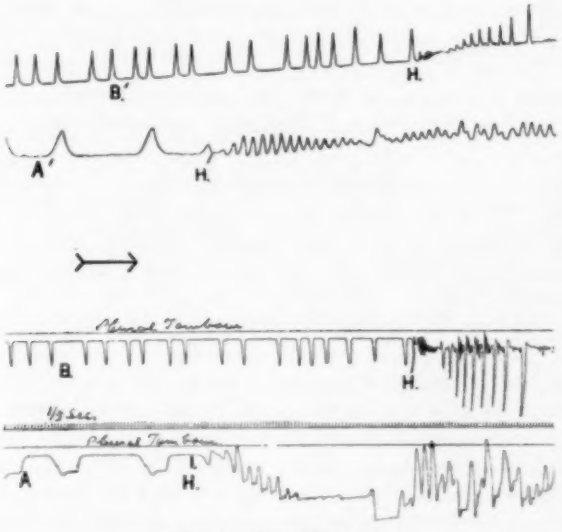

Fig. 4.—Experiment 4.

Experiment 4.—In Figure 4 there is a tracing from an experiment which was designed to show the intrapleural pressure during the period of the histamin effect, with the idea that, if histamin produced a decided bronchiolar hypertonus, then there should be a lessened respiratory excursion in the presence of a lowering minus pressure within the pleural cavity. In this experiment the plethysmograph was not used. The animal breathed through a tracheal cannula directly into the Benedict reservoir. The tracing reads from left to right, and the time-marker is in fifths of seconds. Lines A and A′ were taken simultaneously. The horizontal line marks the line of barometric pressure in the pleural tambour. Line A′ was a simultaneous tracing in the Benedict apparatus.

After the injection of 5 c.c. of 1:10,000 histamin into the jugular vein, the respiratory rate became very rapid and the volume of excursion was very small. To the right it will be seen that, during the period in which the pleural tracing

showed a very great descent in pressure, the volume of tidal air in the lung diminished. In fact, when the excursion of pleural pressure was very considerably extended, from the barometric line to a considerable distance below, the excursion of the lung was quite small. So we are certainly justified in saying that in the presence of a low barometric pressure in the pleural cavity, and also in great excursions of the pressure within the pleural cavity, there was a marked rigidity of the lung.

Line B and B′ are tracings taken from the same animal after a second injection of the same dose of histamin. The beginning of the histamin effect is apparent at H in the tracings both of pleural pressure and of lung excursion. The two experiments show essentially the same thing.

Thus far our investigation has shown that equal tracheal stenosis to inspiration and expiration in both men and dogs failed to produce emphysema. It has also been shown in both men and dogs that, when tracheal stenosis to expiration is greatly in excess of that to inspiration, there is no emphysema. It has further been shown in dogs that, when tracheal expiratory resistance is much greater than resistance to inspiration, emphysema can be induced only with the addition of hyperpnea, as follows of course when the animal is made to rebreathe into a bag containing a high concentration of carbon dioxid.

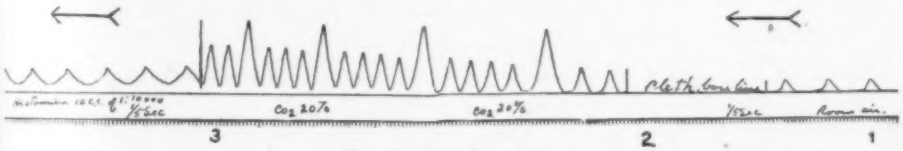

Fig. 5.—Experiment 5.

Furthermore, the experiment in which the tracing of Figure 4 was made proved that, when a general bronchiolar hypertonus was produced by the use of histamin, there was a great lowering of the barometric pressure in the pleural cavity during the entire respiratory cycle, but in spite of it there was a very small respiratory excursion and the total volume of the lung was not increased.

Experiment 5.—An experiment was made for the purpose of tracing the character and volume of the respiratory excursion and measuring the volume of the animal under the effect of a large dose of histamin with an intact thorax. The only operative procedure was the introduction of cannulae into the trachea and the jugular vein, into the latter of which the histamin was injected. The tracing (Fig. 5) should be read from right to left, and is simply the plethysmographic respiratory tracing of a 9 kilo dog. The first part, from 1 to 2, shows the animal breathing atmospheric air, and then at 2, the animal was made to rebreathe into a bag containing 80 per cent. oxygen and 20 per cent. carbon dioxid. Under the influence of hyperpnea thus induced, with perfectly free tracheal cannula, the total volume of the dog was increased about 50 c.c. Then during this period of hyperpnea 10 c.c. of 1:10,000 histamin was injected into the jugular vein, and immediately, at 3, there followed a great modification in the respiratory excursion. Before the effect of the histamin was apparent and while the animal was rebreathing a high concentration of carbon dioxid, the volume of respirations varied between 500 and 264 c.c. Then before the histamin

took effect, the duration of the respiratory cycle was 6/5 seconds. After the histamin took effect, the volume of the respiration was 110 c.c., and the time of a respiratory cycle was 13/5 seconds, the expiratory and inspiratory phases having exactly the same duration. It is quite apparent from the prolongation of both inspiration and expiration, with a great diminution in the volume of the tidal air, that the animal was breathing against a great resistance in both inspiration and expiration, and although in this experiment there is no tracing of the intrapleural pressure, I believe we are justified in assuming from our former experiments that the animal was employing a vigorous respiratory effort. *The tracing shows that the volume of the dog was not increased, although the bronchiolar spasm was induced at a time when great hyperpnea was demanded by rebreathing 20 per cent. carbon dioxid; and just as we have seen in our patients with severe bronchiolar spasm when active expiration was demanded, inspiration and expiration are of equal length.*

This experiment, in the light of all the preceding observations, offers very conclusive evidence that a uniform hypertonus throughout the bronchial tree will not prolong the expiratory more than the

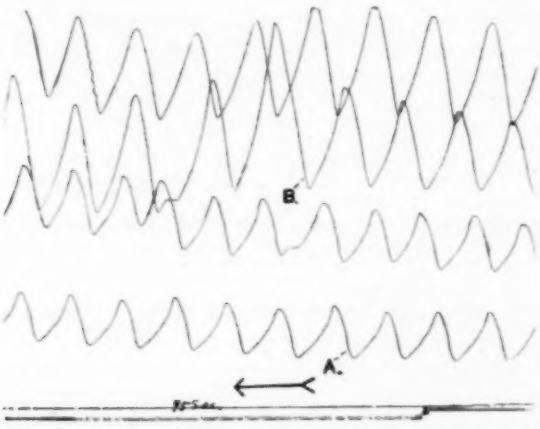

Fig. 6.—Case 9. Bronchiolar spasm not preceded by bronchitis.

inspiratory phase and will not produce emphysema. Furthermore, in the experiment from which the tracing in Figure 3 was made, there is very satisfactory evidence that active compression of the lung does not create a vicious expiratory cycle by compressing the outlet of the respiratory units, as the Biermer theory demands.

The following case offers clinical confirmation of the foregoing statements:

Case 9.—The tracing shown in Figure 6 was made from a young, vigorous man, who had an attack of bronchiolar spasm which was not preceded by bronchitis, and so far as we are able to determine, the bronchiolar hypertonus was a symptom of anaphylaxis from hay fever and not a hypertonus of the bronchial musculature which could be traceable to any nervous excitation within the bronchial tree or within the mediastinum. There was a considerable

amount of nasopharyngeal irritation. The results of the tracing, which was made during his period of bronchiolar spasm and continued after epinephrin was given hypodermically until he had perfect respiratory relief, present very good evidence that in clinical experience we may have bronchiolar hypertonus which will greatly reduce the vital capacity of the lung and not increase its residual air. In fact, we have in this patient with a uniform bronchiolar hypertonus quite the same results so far as the vital capacity and lung volume are concerned as has been shown in dogs when bronchiolar hypertonus was induced by intravenous injections of histamin.

This patient went to bed with perfect respiratory comfort, and was awakened in the middle of the night by a feeling of great respiratory discomfort. Inasmuch as the patient was one of the interns on the medical service in Lakeside Hospital, he was very conversant with the methods of studying respiratory phenomena, and was able to give ideal cooperation. The tracing should be read from right to left. The time marker is in fifths of a second. The two lower lines were traced before the effect of adrenalin was apparent, and the two upper lines were traced after the bronchiolar hypertonus had been relieved by hypodermic injection of 1:1,000 epinephrin.

Before epinephrin was given, the vital capacity of his lung had been 2,699 c.c. seated, and 1,932 c.c. recumbent. After the effect of epinephrin was produced, the vital capacity was 4,264 c.c. seated, and 3,893 c.c. recumbent. The respiratory rate before epinephrin was 18 per minute, and afterward 14. Before epinephrin there was a great abundance of fine and coarse sibilant râles over each portion of both lungs, but after epinephrin all traces of adventitious sounds disappeared. His sense of discomfort was purely on the inspiratory side.

Expiration was a passive procedure, involving no contraction of the abdominal muscles. The patient said that on former occasions he had had attacks much more severe and exhausting, and during them he had been compelled to employ the abdominal muscles during expiration.

In the lower line at A, the duration of the respiratory cycle is 18/5 seconds. The duration of inspiration is 6/5 seconds, and as will be noted in the tracing of the inspiratory phase, the up stroke shows a drag toward the left after the top of the excursion is approached. In other words, there is evidence of a slowing of the volume flow toward the end of the inspiratory excursion. The expiratory phase lasted 12/5 seconds, just double the duration of the inspiratory phase, and the amount of air expelled during the 12/5 seconds was 374 c.c. At B, after the bronchiolar hypertonus had subsided, we find a respiratory cycle which lasted 24/5 seconds, the duration of inspiration being 11/5 seconds and the expiratory phase 13/5 seconds, and the amount of air expelled was 2,210 c.c. So, before epinephrin was given 324 c.c. were passively expelled in 12/5 seconds, and after epinephrin was given 2,210 c.c. were passively expelled in 13/5 seconds. In spite of the fact that the vital capacity during the attack of bronchial spasm was lowered over 1,500 c.c., there was evidence of only a very slight increase in the volume of the lung. Before epinephrin the lower border of the lung was in the ninth interspace in the axillary line, and after epinephrin it was in the eighth interspace; and during the attack, although his diaphragm was coordinately activated with his intercostal muscles, all of both costal margins moved in an outward direction during inspiration. So we are justified in saying that the reduction in vital capacity was not traceable to an increase in residual air in the lung, but was due purely to bronchial stenosis.

Dr. L., from whom the tracing was taken, has repeatedly tested his vital capacity during the past year and has always found it to be about 4,000 c. c. In fact, the character of Dr. L.'s tracing shows his respiratory excursion during the attack to be quite like the respiratory excursions found in dogs when an equal tracheal stenosis to inspiration

and expiration is employed. After the attack was over, there was not the slightest evidence of any kind for bronchitis or any modification in the extensibility of the lung.

REGIONAL EXPIRATORY DYSPNEA

At a stage of the investigation when the relation between bronchiolar hypertonus and pulmonary emphysema seemed very elusive, a patient came into Lakeside Hospital who presented a group of symptoms that I had never before seen.

CASE 10.—This man had an aneurysm of the aorta involving the latter portion of the ascending and the first portion of the transverse arch. The first part of his aorta showed no evidence of dilatation. All the physical signs and the roentgenograms confirmed the diagnosis of an aneurysm which lay in front and above the left bronchus and showed no evidences of contact with the right bronchus. In all cases of obstruction of the bronchus from aneurysm which had come under my observation, there was an equal obstruction to inspiration and expiration, and there never had been in former cases any difference in degree of obstruction when the patient was seated or recumbent. This man, however, showed a very curious phenomenon. When he was in the upright position, there was no demonstrable stenosis to the left bronchus, but when he was on his back, there were decided evidences of stenosis to this bronchus, and during expiration it was much greater than during inspiration. The man suffered no pain and no great discomfort when he was going about. His complaint was that when he lay down he had an uncomfortable, "stuffy" feeling over the left side of his chest.

Physical examination revealed very characteristic signs of aneurysm of the arch of the aorta. When he was in the upright position, the respiratory excursions of the two sides of the thorax were nearly equal, but when he was lying down, the left side became distinctly larger than the right, and the respiratory excursion of the entire left side was very much less than on the right. Palpation revealed comparative immobilization of the ribs of the left side during inspiration in this position, and over the left hypochondrium there was an absence of the piston thrust from the left leaf of the diaphragm, whereas the right side of the diaphragm had a perfectly normal and very active excursion. The costal margin of the left side moved very slightly in an outward direction during inspiration, and percussion revealed a decidedly lower position of the left lung in the axillary line.

When the patient was upright, the respiratory sounds on the two sides of the thorax were equally loud, but when he lay down, those on the left side were only faintly audible. There was also much less tactile fremitus on the left side.

When he was seated, his vital capacity was 3,711 c.c.; lying down, 2,545 c.c.—a difference of 1,166 c. c., which is a far greater disparity than one will find in any other condition, for few persons will on lying down show a lessening of more than 250 c.c. in their vital capacity.

The pulmonary emphysema of the left side when the patient was recumbent was due to the relation between the aneurysm and the left bronchus. In this position the weight of the aneurysm compressed the left bronchus, but during inspiration the lifting of the thoracic cage permitted a freer flow of air into the right lung than that allowed out of the left lung during expiration. He was able to compensate for the impairment in ventilation of his left lung by a very moderate increase in ventilation of the right, and therefore had no air hunger. When the man was upright, there was during expiration no demonstrable sign of compression of the left bronchus.

On comparing this case with Case 4, in which there was an expiratory stenosis of the trachea from an aneurysm of the aortic arch, it will be apparent why this latter patient acquired an emphysema of his left lung when he was lying down. One can readily see that the essential difference between the two cases lies in the fact that the patient last referred to had a very decided expiratory dyspnea involving the left lung but none involving the right, whereas in the former patient, although he suffered from severe expiratory dyspnea, both sides of the lung were equally involved because the expiratory compression was applied to the trachea. This suggested the idea that pulmonary emphysema may be traceable to an excess of expiratory obstruction over inspiratory obstruction; and that clinically we find a marked pulmonary emphysema attending the process because the expiratory dyspnea is unequally distributed throughout the bronchial tree, whereas under the influence of histamin our experiments failed to show any emphysema simply because the hypertonus was equally distributed.

The patient with an expiratory dyspnea confined to the left bronchus had a great increase in the residual air of his left lung, which reduced the total capacity of his lungs by 1,166 c. c. This was accomplished without air hunger or hyperpnea or an active expiration, which is the very essential criticism above presented and must be met by a satisfactory theory for emphysema caused by bronchiolar hypertonus. If we conceive of these gross relations of expiratory dyspnea between the two lungs being applied to the terminal bronchioles throughout the bronchial tree, we then have a theory of emphysema from clinical bronchiolar hypertonus which conforms to the facts of clinical experience.

The physical signs produced by an aneurysm of the transverse arch compressing the left bronchus were very readily reproduced experimentally in the dog by procuring expiratory dyspnea confined to one lung with no obstruction to either bronchus during inspiration.

Experiment 6.—A rubber cork was used, through the middle of which was passed a metallic tube, with a diameter three-fourths that of the cork itself. This cork was just large enough to fill a bronchus of the dog employed. Over one end of the cork was spanned a small strip of rubber dam, and the cork was so inserted into the right bronchus that this end lay in the distal position. During inspiration there was no obstruction to the entrance of air into the right lung, but during expiration there was very pronounced obstruction. Under a pressure equal to 80 mm. of water, the minute volume flow of air through this valve measured 1,200 c.c., which would just about balance the elastic retraction of the dog's lung. Figure 7 shows the animal's thorax when it was comfortably breathing atmospheric air. The disparity in the elevation of the two leaves of the diaphragm was quite like that in our patient with aneurysm when he occupied the horizontal position. When the animal was made to rebreathe a high concentration of carbon dioxid, this disparity was very considerably increased.

If we consider the factors attending pulmonary emphysema as a result of bronchiolar hypertonus, we shall see that the following must be considered: (1) There is always dyspnea, but it is not necessarily so pronounced as to cause great discomfort. (2) The process is not accompanied by hyperpnea. Even in the very severe cases, the minute

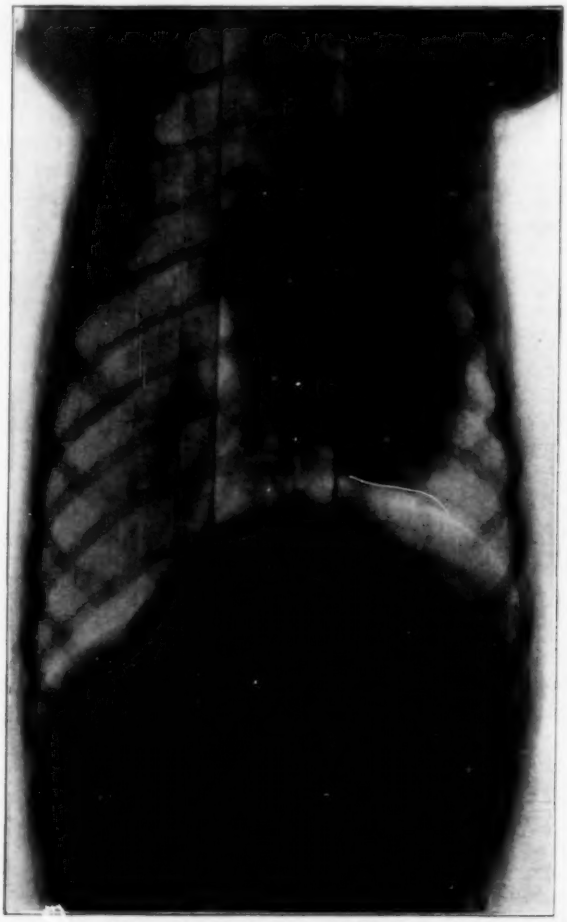

Fig. 7.—Experiment 6. Thorax of dog in which an aneurysm of the transverse arch was produced experimentally.

volume of air is not increased more than 25 per cent. (3) An active expiratory phase is not essential for the production of emphysema.

An unequally distributed expiratory dyspnea would satisfy all these criticisms, as shown in our patient with expiratory dyspnea restricted

to the left side, and the dog with expiratory dyspnea restricted to the right side. From our experimental and clinical observations, therefore, it seems reasonable to suppose that in the acute cases an unequal distribution of the expiratory dyspnea is essential for the production of emphysema. In the chronic atrophic cases also it is known to be unequally distributed.

This study does not pretend to offer a satisfactory solution of the problem of pulmonary emphysema. As in massive collapse of the lung, which is also dependent upon some effect on lung motility, our present knowledge of physiology is not sufficient for a satisfactory explanation. This study does, however, reveal the inadequacy of the commonly accepted theory of emphysema, and justifies the suspicion that an unequal distribution of expiratory stenosis throughout the bronchial tree is the essential factor.

SUMMARY

1. Though active expiratory compression of the lung is rarely employed, the vigor with which the expiratory muscles can compress the lungs is greater than that with which the inspiratory muscles can distend them. Therefore, the air inspired within a given time can be expired within the same time, provided the resistance in the trachea or the branches of the bronchial tree is the same in inspiration as in expiration.

2. When the tracheal or uniform bronchial resistance to expiration exceeds that to inspiration, the residual air in the lung is increased only when hyperpnea attains such a degree that the respiratory need will not allow adequate time for the volume of the expired air to equal that of the inspired air.

3. Compression of the lungs in expiration does not produce a vicious cycle of increasing resistance to expiration.

4. Neither hyperpnea nor an active expiration is essential for the production of emphysema.

5. Prolongation of expiration in emphysema does not measure the degree of expiratory resistance, but indicates the patient's respiratory tolerance of prolongation of the expiratory phase. It is only in the extremity of respiratory needs that active expiration is employed to overcome expiratory resistance.

6. In bronchiolar spasm severe enough to demand an active expiration, the inspiratory and expiratory phases have the same duration and the volume flow within each phase is constant.

7. That an excess of expiratory over inspiratory resistance should produce emphysema, the excess must be unequally distributed in the bronchial tree.

A STUDY OF MICROLYMPHOIDOCYTIC LEUKEMIA

WITH THE REPORT OF A CASE *

SOLOMON FINEMAN, M.D., M.A.

MINNEAPOLIS

PART 1

In 1915, Citron [1] reported a case of leukemia which from the blood picture and clinical findings, was diagnosed as "micromyeloblastic leukemia." The postmortem histologic study carried out by Pappenheim and Citron showed that the bone marrow was entirely normal. However, the cells of the follicles, as well as the cells of the interfollicular tissue of the lymph nodes and spleen, contained a slightly enlarged, eccentrically placed, perfectly round nucleus which resembled very closely the nucleus of a "myeloblast." The largest forms, however, were not as large as those found in "myeloblastic leukemia."

While the blood showed a definite myelogenous picture, it was evident that the "myeloblasts" and "micromyeloblasts" of the blood were not coming to any extent from the bone marrow because the bone marrow was normal (Pappenheim and Citron). On the other hand, there was clear evidence that an actual proliferation in situ of the follicular as well as of the interfollicular tissue was taking place, and, furthermore, that there was an actual metaplasia of lymphocytic cells into "micromyeloblastic" cells. Citron's conclusion, therefore, was that the "micromyeloblastic" cells of the blood were being generated in the follicles and interfollicular tissue of the lymph nodes and spleen and that these "micromyeloblastic" cells were passing from the follicles into the blood stream. Citron regarded his case as being of utmost significance in that it was the first case on record which would seem to prove that the dualistic doctrine of the origin of white blood cells, namely, the complete independence of the origin of myeloid and lymphoid blood cells, did not always hold true.

Citron's case was one which anatomists and hematologists had long been seeking. It offered partial evidence in contradition to the statements made by Naegeli, Schridde, Meyer, Hyneke and Ziegler [2] and other dualists that "myeloid tissue" has never been observed proliferat-

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* A thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Arts.

1. Citron, J.: Ueber zwei bemerkenswerte Fälle von (akuter) Leukämie. Folia haematol. **20**:1, 1915.

2. Naegeli, Schridde, Meyer and Hyneke, and Ziegler: Quoted by Ehrlich, P., and Lazarus, A.: (Rewritten by A. Lazarus and O. Naegeli, and translated by H. Armit). Anemia, New York, Rebman Co., 1910, p. 148.

ing in the germinal centers of spleen or lymph node follicles; that in all cases showing "myeloid infiltration" of the spleen or lymph nodes the follicles are passive or atrophied.

This case shows not only a proliferation of the lymph node follicles but what is of utmost significance, a proliferation of "micromyeloblasts" and "myeloblasts" in the germinal centers of these proliferating follicles. Although a necropsy was not permitted, we were fortunate in obtaining a lymph node during the patient's life. This lymph node was fixed in Helly's fluid immediately after excision, so that the material studied was obtained under ideal conditions.

In brief, we had a case of leukemia in which the blood contained enormous numbers of cells, which ordinarily would be called "the rare micromyeloblasts." The blood picture would lead one to make a diagnosis of myelogenous leukemia. Clinically, however, we had evidence pointing to lymphopoietic activity, namely, a mediastinal tumor, as revealed by percussion and roentgenograms, a very marked enlargement of lymph nodes over the entire body, and a markedly enlarged spleen.

That the lymphopoietic organs were very active was proven by the sections of lymph node, which showed that the blood cells referred to as "micromyeloblasts" were in reality proliferating right in the lymph follicles and germ centers of the node, and could be traced entering the circulation from the lymph node.

I believe, therefore, that our case offers strong evidence that the unitarian theory of the origin of white blood cells, which will be discussed later, is the correct one.

REPORT OF CASE

History.—Service of Dr. E. T. F. Richards. Patient, a girl, aged 17, single, American of Swedish descent, came to University Hospital Jan. 20, 1919.

Present Complaint.—Weakness and rapidly enlarging masses in the neck and axillae.

Family History.—Negative.

Social and Occupational History.—Negative.

Past History.—She has been well up to four weeks ago (December, 1918). She had measles at the age of 6; no sequels; scarlet fever at 15; no sequels; tonsillitis, acute, at 16; lasted four days; could not swallow without pain. No enlarged glands at that time. Felt fine after attack subsided.

Head: *Eyes.*—She has had "eyestrain" for the past four months (October, 1918, to January, 1919) and wore glasses, with relief; vision is good. *Ears.*—Negative. *Nose.*—Occasional "cold"; otherwise negative. *Mouth and Throat.*—Teeth filled during summer of 1918.

Cardiorespiratory: Negative.
Gastro-Intestinal: Negative.
Genito-Urinary: Negative except occasional nocturia.
Catamenia: Began at 15; negative.
Venereal: Negative on direct and indirect questioning.
Neuromuscular: Negative.
Skin: Negative.

Habits: Good. Weight: Best in summer of 1918, 135 pounds; now apparently 120 pounds.

Present Illness.—Patient was well until November, 1918; felt "fine and had red cheeks." Beginning in November, 1918, and especially toward the latter part of the month, she began to complain of being tired, especially so after coming home in the evening. Neither the patient nor her mother noticed any paleness at that time nor enlarged masses. Mother did notice, however, that the patient became very fretful and irritable.

Dec. 23, 1918, the patient came home from work and complained of feeling very tired and of having a severe headache and pain in her knees. Mother thought she had "influenza." Patient did not go back to work on account of weakness. Also at that time she noticed a beginning pallor of the face. The pain in the knees subsided after a few days, but the weakness and pallor became progressive. Patient did not go to bed, however, for two weeks. At the end of that time, in the early part of January, she noticed "lumps" in her neck, especially behind and below the ears. Her hearing became impaired, and once, when she blew her nose, she noticed blood on her handkerchief. A physician was called and diagnosed the case as "mumps."

Two days after the appearance of the masses behind and below the ears, the patient noticed a "lump" under the right jaw. This lump enlarged at first and then decreased in size. Three weeks after onset, about January 14, patient noticed "lumps" in both axillae, but none elsewhere. From that time on the swellings gradually enlarged and the mother began to notice a definite progressive paleness.

Patient denied having fever, hemorrhages and sweats. She "caught cold" about four days before entering the hospital and developed a nonproductive cough. On entrance she had no headache; she could read; nasal breathing was free. She had no pains; her appetite was good; bowels were regular, and she slept well.

Physical Examination.—Temperature, 100.6 F.; pulse, 146. Patient in bed; has dry nonproductive cough; voice hoarse; looks very anemic; development and nutrition, good; no edema, cyanosis or jaundice. Neck and sides of face appear swollen with irregular shaped subcutaneous masses.

Head: *Sinuses and Mastoids.*—Tenderness over frontal sinuses and mastoids and over left antrum. *Eyes.*—Eyegrounds show extensive fresh hemorrhages in both retinae and disks; disk margins indistinct but not choked. Sclerae have a slightly yellowish tinge. Conjunctivae are very pale. Visual fields appear to be normal. *Ears.*—Moderate deafness; with watch, right ear, 3½ inches; left ear, one-half inch. Bone conduction greater than air conduction R. and L. *Nose.*—Negative. *Mouth.*—Lips show extreme anemia and capillary pulse is detectable. Gums are also extremely anemic; gingivitis is present. The gums are tender and bleed on pressure. Teeth are very crowded, especially in the upper jaw where one tooth protrudes in abnormal position. Few teeth are carious. Mucosa of mouth is very pale. The palate is very high and arched. The tonsils are very large, glistening, pearly in appearance, so large that they almost occlude the entire pharynx. The tongue is coated.

Glands: Chains and matted masses of glands are felt in these regions: anterior and posterior auricular; submaxillary; anterior and posterior cervical, left and right subclavicular; over both apices anteriorly and posteriorly; over the trapezii; in the axillae and in the inguinal regions. These are all bilateral. They vary in size from that of a small pea to that of a hen's egg. Some are round; some are oval and many are matted. They are hard and not tender to pressure; are freely movable and not attached to the skin. The size of the face is shown in Figure 1. A comparison is made of the size of the glands from day to day in Table 1 and Figure 2.

Chest and Lungs: *Anteriorly.*—Inspection, negative, except that chest comes down rather slowly with expiration. Palpation, negative. Percussion, abnormally wide supracordial dulness (Fig. 3). Auscultation, generalized "cog-wheel" breathing; exaggerated, tubular over area of supracordial dulness. Vocal

fremitus and whispered voice increased over same area. *Posteriorly.*—Inspection, small masses over both trapezii. Palpation, negative. Percussion, diminished resonance for 5 cm. to right and left of vertebrae on levels I to VI D. Auscultation, cog-wheel breathing, generalized. Tubular breathing from I to VI D. for 5 cm. to right and left. Vocal fremitus and whispered voice increased over spine from I to VI D. for distance of 5 cm. to the right.

Breasts: Negative.

Spine: Increased whispered voice and dulness to sixth dorsal vertebra. Costovertebral angles, negative.

Heart: Inspection, negative; palpation, negative; percussion, cardiohepatic angle obtuse; absolute dulness increased (Fig. 3).

Fig. 1.—Photograph of patient Feb. 14, 1919. Note large preauricular nodes. See Figure 2.

MEASUREMENTS

Intercostal Space	Right, Cm.	Left, Cm.
2	3	4
3	2	6
4	3	7
5	4	8

Auscultation Sounds.—Second pulmonic is accentuated; first sound at the apex is accentuated. *Murmurs.*—Systolic murmur, short, transmitted but slightly into axilla, heard at apex, tricuspid and aortic areas and clearest immediately to the left of the sternum. Blood vessels, negative. Pulse, rapid; sharp rise and fall. Blood pressure: systolic, 130; diastolic, 40.

Abdomen: Inspection, negative; palpation, spleen palpable 7 cm. below costal margin in midclavicular line. No notch felt; freely movable with respiration; no tenderness; liver not enlarged. Percussion, splenic dulness same as on palpation. Liver dulness 12 cm. in midclavicular line.

Extremities: Upper, negative, except extreme anemia of nails. Lower, old traumatic scar on left thigh, otherwise negative.

Sensation: Normal. Reflexes: Negative, except that right knee jerk was very sluggish and the left was not obtainable. No cloni; Babinski, Gordon or Oppenheim signs. Vibration Sense: Present over all bony prominences. Rectum, negative.

Laboratory Data on Entrance.—Urine: trace albumin; sp. gr., 1.010; acid; few leukocytes and few hyalin casts; Bence-Jones body negative. Guaiac test repeatedly negative. Sputum: negative. Stool: negative repeatedly for blood with guaiac test.

Blood: hemoglobin, 29 per cent. (Dare); red blood cells, 1,900,000; white blood cells, 99,000. Differential count (Table 4 and Fig. 4).

Phenolsulphonephthalein excretion, 66 per cent. in two hours. Blood Wassermann negative.

Blood Chemistry: Sugar, 0.105 per cent.; creatinin, 1.40 mg.; urea nitrogen, 10.50 mg.

Blood culture negative.

Mosenthal test negative. For metabolic studies with excreta in urine and feces see Tables 2 and 3. Electrocardiograph tracing: negative.

PROTOCOL

All white and red cell counts and hemoglobin determinations were done by Dr. Swan Erickson and myself. We used the same set of pipets throughout, and on numerous occasions checked each other and followed as closely as possible the same technic throughout the patient's stay in the hospital. In referring to spleen and liver measurements, we mean measurement in the midclavicular line below the costal margin.

Jan. 21, 1919: Hemoglobin, 29 per cent. (Dare). Red bl[illegible]lls, 1,900,000; white blood cells, 99,000.

January 22: White blood cells before roentgen-ray tr[illegible]ment, 44,000. Roentgen-ray treatment over glands of chest and neck.

January 23: Glands diminished to from one-fourth to one-sixth of their previous size. Mediastinal width 8 cm. Tonsils only half as large. White blood cells, 9,600.

January 24: White blood cells, 4,800.

January 25: Transfusion of 200 c.c. blood; no reaction; clinical improvement marked.

January 27: Glands, smaller than on January 23. Tonsils only about one-sixth of former size. Spleen, 3 cm. Mediastinal dulness diminished.

January 30: Right and left posterior auricular glands enlarging; hearing diminishing. White blood cells, 33,000 at 11 a. m.; 50,000 at 6 p. m.

January 31: Glands enlarging again; spleen 7 cm. White blood cells, 50,000.

February 1: White blood cells, 8000; spleen, 4 cm. Mediastinal dulness, 5.5 cm. Transfusion of 300 c.c. blood.

February 3: White blood cells, 9,000.

February 4: Distinct swellings in front of right and left ears. Tonsils enlarging; some of other glands enlarging. White blood cells, 26,800 at 11 a. m.; 49,000 at 6 p. m.

February 5: White blood cells, 70,300. Difficulty in breathing present; restless; hearing poorer. Tonsils markedly enlarged; lacked 1 cm. of meeting in midline. Spleen 7 cm. All glands definitely enlarged.

February 6: White blood cells, 90,000; no reticulated cells; platelets, 90,000 per cubic millimeter.

February 7: White blood cells, 72,000; axillary lymph gland excised.

February 8: White blood cells, 42,000 at 10:30 a. m.; 68,000 at 7 p. m. Patient's general condition worse in evening; dyspnea; nasal breathing impossible. Tonsils, 0.5 cm. apart. Facial and axillary glands enlarged. Spleen, 7.5 cm. Supracordial dulness, 8.5 cm. in second intercostal space.

February 10: White blood cells, 60,000; patient's general condition the same.

February 11: White blood cells, 89,000.

February 12 and 13: Practically no change in patient's general condition. White blood cells, 108,000.

February 14: White blood cells, 108,000 at 9:30 a. m.; 68,000 at 2 p. m. The third roentgen-ray treatment was given at 2:30 p. m. over the neck, tibia and femurs. Patient dyspneic; dilated veins over temples. Mass of glands on right side of face, 8 cm. in diameter; left, 7 cm. These masses are palpable from back of the ears to the angle of the eye. They are very prominent. The tonsils and uvula practically obstruct nasopharynx. Nasal breathing impossible. Spleen, 9.5 cm.

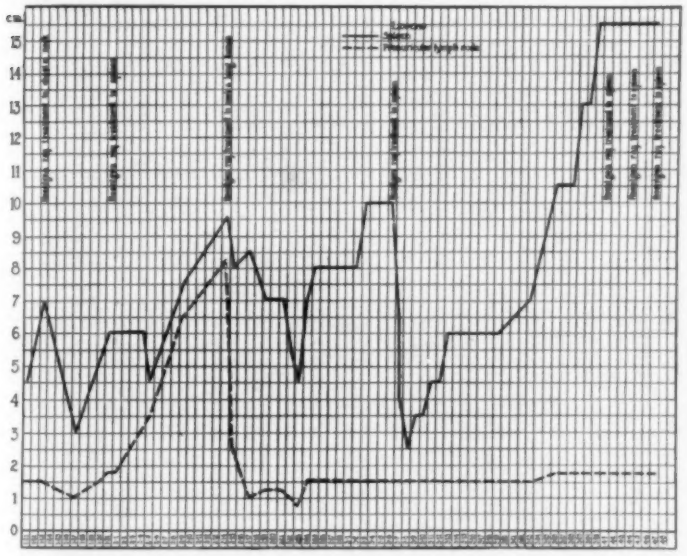

Fig. 2.—Shows variations in size of preauricular lymph nodes and spleen in relation to roentgen-ray therapy. Scale in centimeters shown on left. Splenic tumor measured below costal margin in midclavicular line.

February 15: Masses in front of both ears are barely visible. Patient breathing freely through nose. White blood cells, 29,300 at 10:25 a. m. Clotting and bleeding time, 5 minutes each.

1:30 p. m.: transfusion of 400 c.c. Felt stronger immediately after transfusion. Facial glands still smaller; not visible, just barely palpable as flat masses about 2 cm. in diameter. Tonsils about 1.5 cm. apart. Spleen, 7.5 cm.

February 17: White blood cells, 10,000. Facial mass on right side not palpable at all; on the left just barely palpable. Tonsils about 2.5 cm. apart. Patient "feels fine." Hemoglobin and red blood cells approximately the same as on entrance. Onset of epistaxis and appearance of numerous petechiae on both legs, from 2 to 3 mm. in diameter.

February 18: White blood cells, 20,000.

February 19: Condition worse. Hemoglobin, 26 per cent. (Fleischl); red blood cells, 1,860,000; white blood cells, 140,000 at 3 p. m.; 208,000 at midnight. Headache all day; constant dull abdominal pains; slow epistaxis all day. Complained of dimmed vision. Numerous fresh petechial hemorrhages on legs with several large bluish areas from 2 to 3 cm. in diameter. Edema of feet. Pressure over sternum, skull, humeri, ulnae, radii, femurs and tibiae elicited exquisite pain. For the first time numerous mitotic figures were observed in the blood in wet and dry preparations.

February 20: Condition worse. Hemoglobin, 21 per cent. (Dare); red blood cells, 1,344,000; white blood cells, 242,000. Glands seemingly not enlarged. Transfusion of 200 c.c. Pulse weak and irregular, thready; rate, 160. Fifteen minims benzol by mouth. Blood chemistry: sugar, 0.117 per cent.; creatinin, 0.75 mg.; urea nitrogen, 9.188 mg.

February 21: Eight minims benzol by mouth in the morning. White blood cells at 9:30 a. m., 62,000; at 1 p. m., 44,000. Blood culture negative. Blood of patient injected into rabbit's ear vein. Nitrogen intake, 9.6 gm.; output, 16.8 gm. in urine. Blood chemistry: blood sugar, 0.099 per cent.; creatinin, 0.60 mg.; urea nitrogen, 9.96 mg.

February 22: Spinal puncture, 20 c.c. clear fluid under pressure; Nonné negative; cell count, 3 per cubic millimeter. Colloidal gold test negative; Wassermann +. General condition good. White blood cells, 6,800. Lymph nodes in general smaller. Bone tenderness diminished. Several epistaxes during day.

February 23: Condition further improved; patient smiling, cheerful, laughed, insisted on being allowed to sit up in chair. Vision definitely impaired; could barely see large newspaper headlines, and small type not at all. Glands and spleen somewhat smaller.

February 24: Condition worse; headache; anxious expression; lips seemed paler; spleen and some of glands enlarged somewhat. White blood cells, 10,000.

February 25: Spleen still further enlarged; glands about the same. White blood cells, 44,000; platelets, 92,000.

February 26: White blood cells, 82,000; 23 minims benzol by mouth.

February 27: White blood cells, 76,000; 23 minims benzol by mouth.

February 28: White blood cells, 34,200; hemoglobin, 13 per cent. (Dare); red blood cells, 900,000; felt fine; asked for second helpings of her meals. Benzol discontinued.

March 1: White blood cells, 22,000.

March 2: White blood cells, 61,000. Condition worse; epistaxis in morning; glands and spleen about the same.

March 3: White blood cells, 105,000 at 1 p. m. Condition worse; severe headache. White blood cells, 176,000 at 7 p. m. Profuse epistaxis in the morning. Lymph glands about the same. Spleen 10 cm. and reached to umbilicus; not tender and no rub felt. Liver, 7 cm.; pulse, from 140 to 170; gallop rhythm. Mitotic figures observed in both wet and dry preparations of blood. Transfusion of 160 c.c. followed by hypodermic of morphin sulphate, ⅙ grain, and atropin sulphate, $\frac{1}{150}$ grain.

March 4: White blood cells, 95,000 at 2 p. m.; 106,000 at 7 p. m.

March 5: White blood cells, 75,200 at 10:30 a. m. Transfusion at 1:45 p. m., 150 c.c.

March 6: White blood cells, 26,300 at 1:30 p. m. Roentgen-ray treatment to spleen at 3:30 p. m.

March 7: White blood cells, 4,000 at 9:30 a. m. Transfusion at 10:25 a. m., 200 c.c.

March 8: White blood cells, 2,300. Spleen by noon just barely palpable. General condition worse. Sight poor; eyegrounds show numerous fresh hemorrhages.

TABLE 1.—Comparative Data from Day to Day Regarding White Cell Count, Changes in White Count Observable on the Same Day; Roentgen-Ray Treatment; Number of Stem Cells Per C.Mm.; Number of Mitotic Figures Per C.Mm., Transfusions, Fluctuations in Size of Splenic Tumor, Tonsils, Facial Glands and General Condition

Date	White Blood Cells	White Blood Cells Later on in Day	Roentgen Ray Treatment	Stem Cells	Mitotic Figures	Transfusion, C.c.	Spleen,* Cm.	Tonsils,† Cm.	Face Glands, Cm.	General Condition
1/21	90,000	.....	.....	1,386	..	...	4.5	0.5	1.5	Fair
1/22	40,000	.....	Cheat-neck							
1/23	9,600	.....	.....	.....	..	...	7	...	1.5	Good
1/24	4,800	.....	.....	271	..	...	...	2		
1/25	5,000	.....	.....	.....	..	200	...	...	...	Good
1/26										
1/27	5,400	.....	.....	.....	..	...	3	3	1	Good
1/28	6,900									
1/29	13,800									
1/30	33,000	50,000	.....	900	..	...	...	...	1.5	Good
1/31	51,000	.....	Spleen	.....	..	...	6	...	...	Fair
2/ 1	8,000	.....	.....	540	..	300	6	2	1.75	Good
2/ 2	9,400	.....	.....	.....	..	...	...	...	1.75	
2/ 3	12,300									
2/ 4	26,300	49,700	.....	.....	..	...	6	1	3	Good
2/ 5	70,200	.....	.....	.....	..	...	4.5	0.75	3.5	Bad
2/ 6	90,000	.....	.....	15,894	+					
2/ 7	72,000	.....	.....	.....						
2/ 8	40,200	68,000	.....	2,160						
2/ 9	65,000	.....	.....	.....	..	...	7.5	0.5	5.5	Bad
2/10	60,000									
2/11	89,000									
2/12										
2/13	108,000									
2/14	108,000	64,000	Neck-bones	31,605	..	...	9.5	0	8	Bad
2/15	29,300	.....	.....	.....	..	400	8	1.5	2.5	Good
2/16	10,300	.....	.....	618						
2/17	10,300	.....	.....	.....	..	...	8.5	2.5	1	Good
2/18	20,000	.....	.....	4,150						
2/19	140,000	208,000	.....	.....	+	...	7	2	1.25	Bad
2/20	242,000	.....	.....	90,800	+	200	7	2	1.25	Bad
2/21	62,000	44,000	.....	8,060	..	...	7	...	1.25	Fair
2/22	6,800	.....	.....	11	..	...	5.5	2.5	1	Fair
2/23	8,500	.....	.....	.....	..	...	4.5	...	0.75	Good
2/24	10,400	.....	.....	.....	..	...	7	2	1.5	Fair
2/25	44,600	.....	.....	.....	..	...	8	...	1.5	Fair
2/26	82,000	.....	.....	45,592	..	...	8	...	1.5	Fair
2/27	76,400	.....	.....	.....	..	...	8	...	1.5	Fine
2/28	34,200	.....	.....	6,498	..	...	...	...	1.5	Fine
3/ 1	22,000	.....	.....	.....	..	...	...	...	1.5	Fine
3/ 2	61,000	.....	.....	.....	+	...	8	...	1.5	Fair
3/ 3	105,000	176,000	.....	50,336	+	160	10	...	1.5	Bad
3/ 4	95,000	.....	.....	.....	+	...	...	...	1.5	Fair
3/ 5	75,000	.....	.....	.....	+	150	...	...	1.5	Fine
3/ 6	26,000	.....	Spleen	.....	..	...	10	...	1.5	Fine
3/ 7	4,000	.....	.....	.....	..	200	4	...	1.5	Fair
3/ 8	2,300‡	.....	.....	153	..	...	2.5	...	1.5	Fair
3/ 9	3,400	.....	.....	.....	+	...	3.5	...	1.5	Fair
3/10	5,600	.....	.....	.....	..	150	3.5	...	1.5	Fair
3/11	5,600	.....	.....	.....	..	...	4.5	1	1.5	Fair
3/12	8,800	.....	.....	.....	..	...	4.5	...	1.5	Fine
3/13	8,100	.....	.....	.....	..	...	6	...	1.5	Fine
3/14	7,000	.....	.....	.....	..	...	6	...	1.5	Fine
3/15	7,900	.....	.....	.....	..	...	6	...	1.5	Fine
3/16	9,600	.....	.....	.....	..	...	6	...	1.5	Fine
3/17	7,000	.....	.....	.....	..	...	6	...	1.5	Fine
3/18	6,000	.....	.....	.....	..	...	6	...	1.5	Fine
3/19	6,900	.....	.....	.....	..	200	6	...	1.5	Fine
3/20	5,900	.....	.....	.....	..	...	...	...	...	Fine
3/21	6,000	.....	.....	100	..	...	...	...	...	Fine
3/22	12,700	.....	.....	.....	..	...	...	...	...	Fine
3/23	17,000	.....	.....	.....	..	...	7	2	1.5	Fine
3/24	17,300	.....	.....	.....	..	...	...	...	...	Fine
3/25	25,500	.....	.....	.....	..	...	...	...	...	Fine
3/26	34,000	.....	.....	.....	..	...	10.5	...	1.75	Fine
3/27	80,000	.....	.....	.....	+	...	10.5	...	1.75	Fair
3/28	115,000	.....	.....	.....	+	...	10.5	...	1.75	Fair
3/29	247,000	178,000	.....	32,505	+	300	13	2.5	1.75	Bad
3/30	260,000	295,000	.....	.....	..	...	13	...	1.75	Bad
3/31	334,000	.....	.....	.....	+	...	15.5	...	1.75	Fair
4/ 1	480,000	.....	Spleen	.....	+	300	15.5	...	1.75	Fair
4/ 2	500,000	.....	.....	75,800	+	...	15.5	2	1.75	Bad
4/ 3	485,000	.....	.....	.....	+	...	....	...	1.75	Fair
4/ 4	578,000	.....	Spleen	.....	+	...	....	...	1.75	Good
4/ 5	545,000	.....	.....	.....	+	200	....	...	1.75	Fair
4/ 6	541,000	.....	.....	.....	+	...	15.5	...	1.75	Fair
4/ 7	646,000	.....	Spleen	2,584	+	...	15.5	...	1.75	Fair
4/ 8	.....	.....	.....	.....	..	...	....	...	....	Died

* Splenic tumor palpable below the costal margin in the midclavicular line.
† Approximate distance between the tonsils.
‡ Lowest white count recorded.

March 9 to 21: The next thirteen days the white cell count and the patient's general condition simulated a lull before an impending storm. The white count varied from 5,000 to 9,000. The patient felt fairly well and even insisted on getting out of bed. We gave her her eighth and ninth transfusion of 350 c.c. of blood in all. Epistaxis occurred frequently. Blood culture was again negative. The glands remained stationary. The tonsils enlarged somewhat and the spleen measured 7.5 cm. March 13. From then on to March 21 the spleen remained stationary.

March 11: White blood cells, 5,600. Basal metabolism, +20 per cent.

March 14: White blood cells, 7,000. Basal metabolism, +7 per cent.

March 22: White blood cells, 12,000. General condition same.

March 23: White blood cells, 17,000. Complained of poor vision; facial glands enlarged slightly. Spleen 8.5 cm. Basal metabolism, +29 per cent. Patient restless.

March 24: White blood cells, 17,300; felt fine; sat up in chair. Spinal fluid: normal pressure; Nonne negative; cell count, 1 per cubic millimeter; colloidal gold test negative; Wassermann negative.

March 25: White blood count, 25,000. General condition good.

March 26: White blood cells, 34,000. General condition good; sat up in chair; facial glands little more enlarged. Mediastinum 7.5 cm. on percussion. Spleen, 10.5 cm. on palpation.

March 27: White blood cells, 80,000. Condition worse; felt miserable; sat up very little; complained of dull abdominal pain; pulse very rapid and heart had gallop rhythm.

March 28: White blood cells, 115,000. In bed all day; anxious expression; ankles and feet edematous; suppuration set in under nail of left big toe; hearing diminished; missed third menstrual period.

March 29: White blood cells, 247,000 at 10 a. m. At 10:38 a. m. transfusion of 300 c.c. White blood cells, 185,000 at 1:45 p. m. Spleen, 15 cm. and beyond umbilicoxyphoid line. White blood cells, 178,000 at 4:10 p. m. Liver, 6 cm. Abdominal pains severe. Ankles and feet more edematous.

March 30: White blood cells, 260,000 at 11 a. m.; 295,000 at 5 p. m. Spleen larger (Fig. 5).

March 31: White blood cells, 334,000. Severe abdominal pain—upper half. Pressure over spleen and sternum gave exquisite pain. Spleen still larger. Fluid in flanks. Edema of lower extremities increased. Dulness at base of left lung posteriorly, probably due to enlarged spleen. Pneumonia not demonstrable.

April 1: White blood cells, 480,000 at 10 a. m. Tonsils enlarged, 2 cm. apart; nasal breathing free. Transfusion of 300 c.c. Roentgen-ray treatment of spleen, three minutes only on account of poor condition of patient. Edema of right hand, wrist and sacrum. Patient very stuporous and complained of severe pain over the spleen.

April 2: White blood cells, 500,000. Condition slightly improved.

April 3: White blood cells, 485,000. Condition still better; talkative and bright.

April 4: White blood cells, 578,000 at 2:30 p. m. Roentgen-ray treatment at 1:30 p. m. over spleen. Liver, 10 cm.; tender. Basal metabolism, +29 per cent.

April 5: White blood cells, 545,000 at 4 p. m. Transfusion of 200 c.c. at 11 a. m. Patient felt better; sat up one hour in bed.

April 6: White blood cells, 541,000. Condition worse.

April 7: White blood cells, 646,000 at 2 p. m. Roentgen-ray treatment at 1:30 p. m., 9 minutes to spleen. Frequent severe epistaxis during day, with several emeses of clotted blood. At night breathing became stertorous and at midnight the patient could be awakened only with great difficulty. When awake, she was rational.

April 8: At 12:15 a. m. patient cried out several times, with inspiratory gasps. Pulse at that time was very rapid but of good quality. Death occurred a few seconds later of respiratory failure.

DISCUSSION

1. *Hemoglobin and Red Blood Cells.*—The hemoglobin and red blood cell count remained low throughout and both progressively diminished, in spite of twelve transfusions, a total of 2,760 c. c of blood.

2. *White Cell Count.*—The white cell count showed some extraordinarily sudden, unaccountable fluctuations. The rise or fall of the white cell count during twenty-four hour periods would sometimes be so great that we were obliged to make three or four counts in twenty-four hours to check our findings.

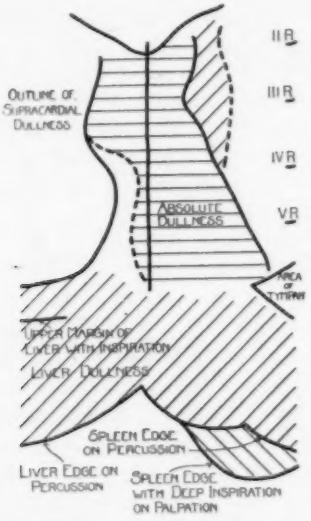

Fig. 3.—Showing percussable mediastinal dulness on entrance to hospital Jan. 21, 1919.

On entrance to the hospital the patient's white cell count was 99,000. In twenty-four hours, before any treatment was instituted, the count fell to 44,000, followed by a further fall after roentgen-ray exposure of the lymph nodes of the neck and mediastinum.

From then on the white cell count kept oscillating between counts as low as 2,300 and as high as 646,000 on the day of death. By making blood counts several hours apart on the same day we were able to demonstrate the following:

January 30: rise of 17,000 white cells in 7 hours.
February 8: rise of 28,000 white cells in 8½ hours.
February 14: fall of 44,000 white cells in 4½ hours.
February 19: rise of 68,000 white cells in 9 hours.

March 3: rise of 71,000 white cells in 6 hours.

March 29: fall of 62,000 white cells in 3 hours.

The rapidity with which a rise or fall of the white cell count would occur in this case was astounding. Thus, we see a rise from 10,500 cells February 17, to 242,000 cells February 20, and just as rapid a fall to 6,800 cells February 22. We see another sudden rise from 22,000 cells March 1, to 176,000 cells March 3, and just as sudden a fall to 2,300 cells March 8. Up to March 8, some of the white cell count fluctuations seemed to occur entirely spontaneously. At times, however, it seemed to us as if the transfusions and roentgen-ray exposures had an immediate effect in causing a drop in the white count. Figure 6, showing the daily blood counts and therapy, would seem to indicate that such was the case.

March 22, the white cell count began to rise with lightning-like rapidity and rose from 6,000 to 646,000 cells in the next seventeen days. From the beginning of this last rise in the white cell count, transfusions, and roentgen-ray exposures had practically no effect on the count, and the patient died with the highest count demonstrable during her stay at the hospital.

On looking over the blood chart (Fig. 6) one is struck by the seemingly periodic exacerbation of the white cell count rise, each period lasting from five to six days. It is of interest to note here that with each rise in the white cell count, the patient's general condition became definitely worse. As a matter of fact, we could usually note a beginning rise in the white cell count by the change in the patient's general condition. During the periods of low count she would be happy and feel so well that she would insist on being permitted to sit up in a chair. As soon as the white cell count would begin to rise, the patient would stay in bed and complain usually of headache and abdominal distress, and she would have an anxious expression.

Krjukow [3] describes a case of "microlymphoidocytic" leukemia in which there were sudden fluctuations in the white cell count, associated with rapid fluctuations in the size of the spleen.

3. *Mitotic Figures.*—A very interesting finding, with counts over 80,000, was the presence of numerous mitotic figures in the blood. These cells, in all stages of mitosis, were easily demonstrable in both the 1 per cent. acetic acid solution, and in the dry stained blood preparations. The higher the count the greater would be the number of mitotic figures. At one time we demonstrated as many as fifteen cells in mitosis in a single field under the low power lens of the microscope and a No. 10 eyepiece.

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3. Krjukow, A.: Ueber einen Fall von akuter Microlymphoidozyten Leukämie, Folia Haematol. **15**:328, 1915.

Gordon Ward [4] describes a "peculiar case of acute leukemia," which from his description might very well have been a case of microlymphoidocytic leukemia, in which he observed as many as thirty-seven mitotic figures per cubic millimeter of blood. Krjukow noted in his case numerous mitotic figures in the blood during the periods of splenic enlargement.

In an attempt to determine whether these mitotic cells, which in all probability were being forced out from the rapidly proliferating lymphatic tissue into the blood stream, would continue the process to completion in vitro, Dr. Swan E. Erickson and I made a study of these cells in 1 per cent. acetic acid solution, physiologic solution of sodium chlorid, 1½ per cent. sodium citrate in physiologic sodium chlorid solution, 1½ per cent. sodium citrate in water, stock blood serum

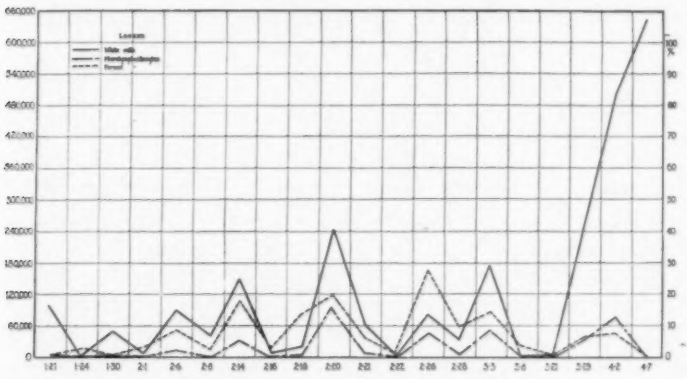

Fig. 4.—Shows relation between the total daily white cell count, total daily microlymphoidocytes, and daily percentage of microlymphoidocytes. Only data obtained during low and high count days are here recorded.

of Groups 2 and 3, and also in patient's own serum, which was of Group 4. We used a warm stage and kept the cells under observation in the above mentioned solutions at body temperature for as long as thirty-six hours. We did not observe a single instance of continuation of the process of mitosis in vitro.

4. *Differential Counts.*—The differential counts gave interesting findings (Table 4). The percentage of the various cells was calculated on a basis of from 300 to 700 cells. The percentage of polymorphonuclear neutrophils varied from as low as 0.4 per cent. to 33.66± per cent. The total number of polymorphonuclear neutrophils was not directly proportional to the relative percentage. For example, with the lowest

4. Ward, G.: A Peculiar Case of Acute Leukemia, Clin. J. **48**:93 (Aug.) 1919; abstr. Folia haematol. **20**:158 (Nov.) 1920.

count of 2,300, the percentage of polymorphonuclear neutrophils was 19.33+ per cent., and the total number of polymorphonuclear neutrophils per cu. mm. was 445. With the highest count of 646,000 the percentage of polymorphonuclear neutrophils was only 1.4 per cent. with an absolute number of 9,044 polymorphonuclear neutrophils per cu. mm. The highest percentage of polymorphonuclear neutrophils, namely, 33.66+ per cent., was present with a total of 6,000 white cells per cu. mm. The number of polymorphonuclear neutrophils per cu. mm. in the normal blood is about 6,000. In this case even with counts as high as 242,000, the total number of polymorphonuclear neutrophils per cu. mm. was only 3,388. Only shortly before death did the absolute number of polymorphonuclear neutrophils go up above the normal, as follows:

March 29: Total white cells, 247,000; polymorphonuclears, 14,820. April 2: Total white cells, 500,000; polymorphonuclears, 9,150. April 7: Total white cells, 646,000; polymorphonuclears, 9,044.

5. *Nucleated Red Blood Cells and Myelocytes.*—Nucleated red blood cells and myelocytes were present in small numbers. These probably were an irritation phenomenon due to the extreme anemia, which at its lowest point gave a hemoglobin percentage of 13 on the Von Fleischl-Miescher instrument, and a red count of only 900,000.

6. *The "Micromyeloblast."*—The most interesting cell was the so-called "micromyeloblast" of Naegeli and Schridde, or the "micro-lymphoidocyte" or "stem cell" of Pappenheim. The total number and relative per cent. of this cell was practically directly proportional to the total count (Fig. 4). With the rise in total white cell count our patient was always clinically worse and the disease could be said to have assumed a more severe aspect. Coincidentally with the increase in the severity of the disease, the "micromyeloblast" would increase in number and percentage, a finding which is similar to the findings of Panton and Tidy [5] in a series of three cases.

With a white cell count of 2,300, the total "micromyeloblast" count was 153. With a white cell count of 500,000, the "micromyeloblast" count rose to 75,800. On the day before death, the total white cell count was 646,000, but the "micromyeloblast" count was only 2,548, probably an exhaustion phenomenon.

7. *Therapy.*—Our therapy consisted of a high carbohydrate diet, roentgen-ray exposure and transfusions. Benzol was tried on two occasions, but in amounts so small and for so short a period of time that its effect can safely be discounted. We have already mentioned the peculiar sudden fluctuations in the white cell count, associated with an

5. Panton, P. H., and Tidy, H. L.: Some Atypical Cases of Leukemia, Folia haematol. **17**:398, 1913.

improvement in the patient's general condition during the periods of low count.

Haughwout and Azuzano[6] report improvement in forty-eight hours following the administration of benzyl benzoate. They suggest, however, that this may be a normal fluctuation of the disease.

The roentgen-ray treatment varied a great deal in its effect on the enlarged spleen and lymph nodes, and on the white cell count. Seven treatments were given by Dr. Frank S. Bissel. The white cell count diminished after each treatment, with the exception of the treatments given a few days before the patient's death, at which time the count rose from 6,000 to 646,000. It must not be forgotten, however, that

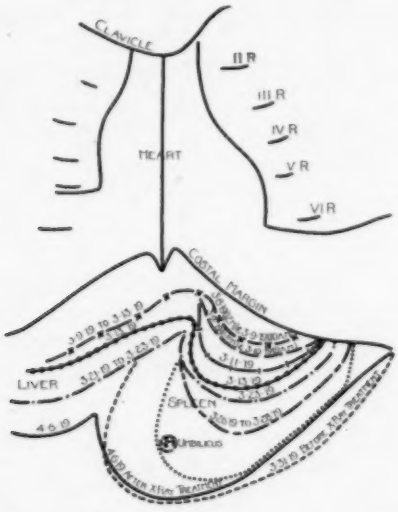

Fig. 5.—Composite tracing of spleen and liver from March 9 to April 6. Note gradual enlargement of both. Compare with Figure 20 showing gradual diminution of splenic dulness.

on six occasions there occurred diminutions in the count, varying from 44,000 to 236,000 cells, without roentgen-ray treatment.

The transfusions also had a varied effect on the patient. They were twelve in number and we gave a total of 2,760 c.c. The hemoglobin and red cell count gradually diminished. In the beginning it seemed as if the transfusions might be a factor in lowering the white cell count and improving the patient's general condition. The

6. Houghwout, F. G., and Azuzano: Notes on the Treatment of a Case of Lymphatic Leukemia with Benzyl Benzoate, New York M. J. **110**:180 (Aug.) 1919.

last few transfusions seemed to have had no effect whatever on the patient. With the first few transfusions there were very severe reactions. We were able to eliminate these reactions practically entirely by the use of small doses of morphin and atropin, given immediately after the transfusions.

An interesting finding during the last few days of the patient's life was the peculiarly changed morphology of the red blood cells. Whereas at the beginning the great majority of cells were very pale and irregular in size and shape, toward the end of the patient's life; the majority of cells appeared like perfectly normal red blood cells. Our impression was that these were functionating transfused cells, and that the patient was practically living on the transfused blood. Ashby [7] has shown that transfused red blood cells may functionate in the recipient for thirty days.

8. *Temperature Curve.*—The temperature varied between 96.6 and 104 F. A rise in the temperature was usually associated with a rise in the white count, enlargement of the spleen, lymph nodes and tonsils, and a marked increase in general malaise. The whole picture would suggest an exacerbation of an infective process.

9. *Blood Culture Studies.*—Blood studies on culture mediums and by injection into rabbits were negative. Baar and Kornitzer [8] and several other authors report positive cultures in the blood of leukemic patients. These, however, were usually found just antemortem and were probably due to secondary infections. To date no one has succeeded in transfering human leukemia to laboratory animals. Ellerman and Bang [9] could produce anatomic and hematologic leukemic lesions in healthy hens by injections of cell free Berkefeld filtered organ emulsions of a leukemic hen. Hirshfeld and Jacoby [10] observed spontaneous leukemia in hens and were successful in transmitting the disease through five generations. Schmeisser [11] also observed spontaneous leukemia in fowls and was successful in transmitting it into other fowls. Ellerman [12] claims that a myeloid type of leukemia may occur in one generation

7. Ashby, W.: Some Data on Range of Life of Transfused Blood Corpuscles in Persons Without Blood Diseases, M. Clinics N. America **3**:783 (Nov.) 1919.

8. Baar, V., and Kornitzer, E.: Ein positiver Bakterienbefund bei einem Fall von chronischer myeloischer Leukämie (Myeloblasten Leukämie), Wien. klin. Wchnschr. **32**:857, 1919.

9. Ellerman and Bang: Experimentelle Leukämie bei Hühnern, Zentralbl. f. Bakteriol. **46**:4, 1908.

10. Hirschfeld, H., and Jacoby, M.: Zur Kenntniss der übertragbaren Hühnerleukämie, Berl. klin. Wchnschr. **46**:159, 1909.

11. Schmeisser, H. C.: Spontaneous and Experimental Leukemia of Fowls, J. Exper. M. **22**:820, 1915.

12. Ellerman, V.: Untersuchungen über das Virus der Hühnerleukämie, Ztschr. f. klin. Med. **74**:43, 1914.

and a lymphatic type in the next, and that this is highly suggestive that both forms are due to the same infective agent.

10. *Metabolic Studies.*—A. The urine and stool chemistry were studied by Drs. Egerer-Seham and Frances Ford. We could not demonstrate any definite relation between our blood and clinical findings and the chemical findings. Tables 2 and 3 give the findings of only a few days on which high fluctuations in white cell count and splenic dimensions occurred.

In Krjukow's case the diminution of splenic enlargement was associated with an increased excretion of ureates.

TABLE 2.—CHEMISTRY OF TWENTY-FOUR HOUR SPECIMENS OF URINE

Date	White Blood Cells	NaCl, Gm.	N, Gm.	Urea N, Gm.	NH_3, Gm.	Inorganic Total Phosphates, Gm.	Creatinin, Gm.	Uric Acid, Gm.
1/20/19	99,000	4.09	4.80	....	....	....	....	....
1/24/19	4,800	5.73	5.98	....	....	....	....	....
2/19/19	208,800	0.70	1.86	1.09	0.25	....	0.17	0.10
2/22/19	6,800	4.84	7.21	3.82	0.32	....	1.81	1.93
3/ 2/19	61,000	2.66	5.87	2.49	0.74	0.97	1.90	1.02
3/ 3/19	176,000	2.31	6.24	2.97	1.04	0.53	1.12	0.88
3/ 4/19	106,000	3.78	6.09	3.11	0.85	1.78	1.84	0.99
3/ 7/19	4,000	3.22	9.82	4.77	0.88	2.59	2.21	2.87
3/ 8/19	2,300	2.39	6.23	3.02	1.00	2.20	1.76	3.05
3/ 9/19	5,600	2.41	7.14	3.98	0.87	0.81	1.34	1.88
3/24/19	17,000	1.43	2.01	1.00	0.37	0.05	0.50	0.16
4/ 1/19	480,000	4.06	4.06	3.08	0.48	0.08	0.46	0.25
4/ 2/19	500,000	1.06	3.70	1.02	0.56	....	0.52	0.42

TABLE 3.—CHEMISTRY OF TOTAL TWENTY-FOUR HOUR FECES

Date	White Blood Cells	Inorganic Phosphates, Gm.	Total Phosphates, Gm.
2/27/19	76,400	0.53	2.10
2/28/19	34,200	0.75	1.11
3/ 1/19	22,000	0.66	1.14
3/ 3/19	176,000	0.52	1.58
3/ 4/19	106,000	1.78	2.58
3/16/19	9,600	0.53	0.76
3/24/19	17,300	0.05	0.16

Ordway [13] reports that radium applications over the spleen in leukemia increase the protein and phosphate constituents of the urine.

B. Blood chemistry studies did not yield data that could be correlated in any way with the white cell count variations.

C. Basal metabolism studies were as follows:

March 11: +20 per cent.; white blood cells, 5,600
March 14: + 8 per cent.; white blood cells, 7,000

13. Ordway, T.: Metabolism in Leukemia and Carcinoma During Radium Treatment, J. A. M. A. **73**:860 (Sept. 3) 1919.

March 23: +29 per cent.; white blood cells, 17,000
April 3: +41 per cent.; white blood cells, 485,000

11. *Blood in Feces and Urine.*—Feces and urine showed no chemical or microscopic blood at any time.

12. *Spinal Fluid.*—The first specimen gave a positive Wassermann, but was otherwise normal. Fluid obtained at a subsequent puncture was normal.

13. *Kidney Function.*—The phenolsulphonephthalein excretion, Mosenthal test and blood chemistry (sugar, urea nitrogen, and creatinin) gave normal values.

14. *Spleen.*—At first the spleen did not seem to play much of a rôle in the leukemic process. January 21 it was palpable about 3 cm. below the costal margin in the midclavicular line. From January 21 to March 3 marked fluctuations in the size of the spleen occurred. It was rather a peculiar effect or coincidence that roentgen-ray exposure of the mediastinal, facial and neck lymph nodes was followed by marked diminution in the size of the spleen, followed, however, each time by an enlargement of the spleen greater than on each previous occasion (Figs. 2, 5, 7 and 20).

March 6, the spleen was palpable in the midline of the abdomen and 10 cm. below the costal margin in the midclavicular line. It was again exposed to the roentgen rays, and again, either as a result of the roentgen-ray exposure or simply as a pure unexplainable coincidence, it had reduced in size in forty-eight hours to such an extent that it was just barely palpable (Fig. 20). In this connection it is of interest to note that the white cell count fell coincidently to 2,300 per c.m.

March 8, the spleen began to enlarge again very rapidly (Fig. 5) and by March 31 it was 5 cm. beyond the midline and 16 cm. below the costal margin in the midclavicular line. This rapid enlargement took place in spite of three exposures to the roentgen ray (Fig. 2). The white cell count also did not seem to be influenced by the roentgen-ray exposures and rose from 2,300 to 646,000 on the day of death (Fig. 6).

15. *Lymph Nodes.*—On entrance to the hospital the lymph nodes of the face, neck, axillae, groin and mediastinum were markedly enlarged. Photographs (Figs. 1 and 8) taken before and after roentgen-ray exposures show a remarkable difference in the size of facial lymph nodes. Here, again, it is an open question as to whether these changes were caused by the roentgen-ray therapy or whether they were simply a part of the peculiar unexplainable fluctuations of the lymphopoietic system. Figure 2 shows the relative fluctuations in the size of the facial lymph nodes.

A comparison of Figures 3 and 11 shows a definite diminution in the size of the mediastinal shadow. This diminution occurred within

forty-eight hours after roentgen-ray exposure of the chest. Plates 9 and 10 showed the same thing.

16. *Tonsils.*—The tonsils also seemed to take a very active part in the leukemic process. With rises in the white count and enlargement of the lymph nodes or spleen, they too would enlarge, so much so, that not only would nasal breathing become impossible but even mouth breathing would be very difficult. Roentgen-ray exposure over the face and neck seemed to produce a definite diminution in the size of the tonsils so that the patient could breathe with ease through the nose and mouth (Table 1).

17. *Liver.*—At first the liver was not palpable. Toward the end, it also enlarged and could be palpated 10 cm. below the costal margin in the midclavicular line.

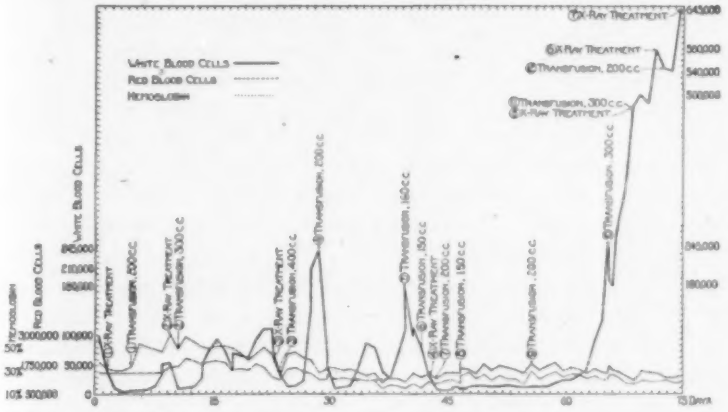

Fig. 6.—Curve of daily white cell count, red cell count and percentage of hemoglobin.

CLINICAL SUMMARY

1. In spite of the twelve transfusions of a total of 2,760 c. c. blood, the patient's hemoglobin percentage and red blood cell count steadily diminished. With a hemoglobin of 15 per cent., on the Von Fleischel Miescher instrument, and a red count of 900,000, the majority of red blood cells were full sized, round, stained well and had every appearance of normal cells. It seems probable, therefore, that the functioning transfused red blood cells prolonged an illness, usually acute and of very short duration.

2. The white cell count showed extraordinary sudden fluctuations. A fluctuation of 70,000 cells in six hours occurred March 29. The blood chart (Fig. 6) shows fourteen additional sudden fluctuations.

3. A study of the blood chart (Fig. 6) shows an apparent rhythmical occurrence of these fluctuations, a seemingly definite cyclic change of from five to seven days' duration.

4. Numerous beautiful cells in all stages of mitosis were demonstrable in the blood, both in the 1 per cent. acetic acid solution and in the dry stained smears.

5. Injection of the patient's blood into a rabbit was negative.

6. Morphin and atrophin, administered after transfusions, eliminated practically all reaction.

7. We could not demonstrate a definitely beneficial effect from roentgen-ray therapy over lymph nodes, spleen and long bones. At first, the spleen diminished in size when roentgen-ray therapy was applied to the chest and lymph nodes or long bones. Whether this was purely coincidental or whether it had any relation to the roentgen-ray therapy, we do not know. One exposure over the spleen was associated with a very pronounced diminution in the size of the spleen, Subsequent roentgen-ray exposures had no effect whatever.

Irradiation of the facial, cervical, axillary and mediastinal lymph nodes by the roentgen ray was followed by marked diminution in their size. Whether this was a direct result of the therapy, or simply coincident with it, is an open question. It is of interest to note that cervical and facial roentgen-ray irradiation was followed by a marked diminution in the size of the tonsils.

8. Enormous rapid fluctuations in the white cell count occurred, which could not be accounted for by therapy.

9. A marked rise in the white cell count was usually preceded and accompanied by a rapid enlargement of the spleen or of some group of lymph nodes.

10. The clinical picture of more or less rhythmically varying white blood cell counts, clinical improvement during the periods of low white cell count, and diminution in size of the lymph nodes or spleen, suggest the possibility of an infectious etiology of the disease.

11. The biopsy of a lymph node showed that at least a great number of "micromyeloblasts," a cell definitely myeloid according to the dualist view, were being generated in the germ center of the lymph node follicles and were passing out from the lymph node into the blood stream. Such a possibility has always been denied by the dualists.

12. Clinically, our case had all the earmarks of a lymphatic leukemia. The blood, however, showed in great numbers a cell, the so-called "micromyeloblast," which is believed by the dualists to originate in the myeloid tissues. To date, the dualists deny the possibility of such a cell originating in the germ center of a lymph node follicle.

A lymph node obtained under the very best possible conditions offers very good evidence in flat contradiction to the dualistic view.

This case is reported, because it offers strong evidence in favor of the unitarian theory of the origin of blood cells.

PART II

MORPHOLOGIC STUDY

Modern hematologists are divided into two strong groups, the so-called unitarians or monophyletists, on the one hand, and the dualists and polyphyletists on the other hand. The bone of contention between these groups is the so-called "stem cell."

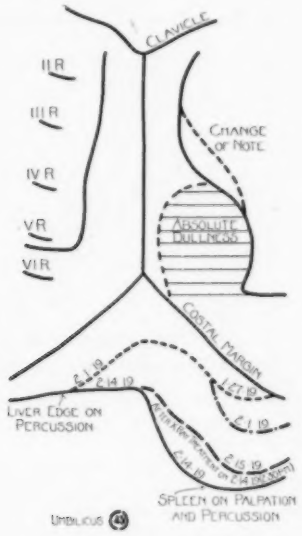

Fig. 7.—Composite tracing showing increase in size of spleen from January 27 to February 14. Slight diminution in size twenty-four hours after roentgen-ray treatment over spleen.

The dualists and polyphyletists consider the lymphopoietic and myelopoietic tissues as two separate tissues, entirely distinct from each other and never interchangeable. They contend that all the cells produced in lymphopoietic tissues come from their own specific stem cells, the "lymphoblasts," and in the same manner all cells produced in myelopoietic tissues come from their own specific stem cells, the "myeloblasts." They claim to be able to demonstrate a difference between "lymphoblasts" and "myeloblasts."

The unitarians or monophyletists deny the specificity of "lymphopoietic" and "myelopoietic" tissues. They present admirable evidence that under certain conditions myeloid cells may be produced by "lymphopoietic" tissues, and, vice versa, lymphoid cells may be produced in "myelopoietic" tissues. Pappenheim and his followers [14] claim that all blood cells spring from a single stem which they call "lymphoidocyte." While some unitarians do not admit that there is a morphologic difference between the "myeloblasts" and the "lymphoblasts," other observers grant such a possibility, but deny the specificity of the mother tissues from which these cells come.

Among the chief exponents of the unitarian theory are Pappenheim,[15] Grawitz,[16] Weidenreich,[17] Maximow,[18] Downey,[19] Ferrata,[20] Du Toit,[21] Arnold,[22] Neumann,[23] May,[24] and Danchakoff.[25] Among the chief exponents of the dualistic and polyphyletic theories are

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14. Pappenheim and Hirschfeld: Ueber akute Myeloide und Lymphadenoide Makrolymphozytäre Leukämie an der Hand von zwei vershiedenen Fällen, Folia haematol. **5**:347, 1908. Pappenheim, A.: Atlas der menschlichen Blutzellen, Jena, 1905-1912. Morphologische Hematologie, Leipzig, Werner Klinkhardt, 1919.

15. Pappenheim, A.: Bemerkungen über artliche Unterschiede, usw., der lymphoiden, Zellformen des Blutes, Folia haematol. **9**: 321, 1909. Clinical Examination of the Blood and Its Technique (translated by R. Donaldson), New York, Wm. Wood Co., 1914.

16. Grawitz, E.: Klinische Pathologie des Blutes, Leipzig, Georg Thieme, 1911.

17. Weidenreich, F.: Die Morphologie der Blutzellen und ihre Beziehung zu Einander, Anat. Rec. **1**:317, 1910.

18. Maximow, A.: Ueber die Zellformen des lockeren Bindegewebes, Arch. f. mikr. Anat. **67**:680, 1906. Ueber embryonale Entwicklung der Blut und Bindegewebezellen bei den Saugetieren, Verhandl. der Anat. Gesellsch, 22, Vers., Berlin, 1908. Experimentelle Untersuchungen zur post fötalen Histogeneses des myeloiden Gewebes, Beitr. z. path. Anat. u. z. Allg. Path. **41**: 122, 1907.

19. Downey, Hal, and Weidenreich, F.: Ueber die Bildung der Lymphocyten in Lymphdrüsen und Milz, Arch. f. mikroscop. Anat. **80**:367, 1912. Downey: The Development of the Histogenous Mast Cells of Adult Guinea-Pig and Cat, and the Structure of the Histogenous Mast Cell of Man, Folia haematol. **16**: 1913. On the Development of Lymphocytes in Lymph Nodes and Spleen, Tr. Minnesota Path. Soc., 1912-1914, p. 91.

20. Ferrata, A.: Le Emopatie, Milano, Societa Editrice Lebraria **1**: 1918. (Reviewed in Folia haematol. **20**: 182, 1920, by Downey.)

21. Du Toit, P. J.: Beitrag zur Morphologie des normalen und des leukämischen Rinderblutes, Folia haematol. **21**:1, 1916.

22. Arnold, J.: Zur Morphologie und Biologie der Zellen des Knochenmarks, Arch. f. path. Anat. u. Physiol. **140**:411, 1895.

23. Neumann, E.: Hematologischen Studien der Leukozyten und Leukämie, Arch. f. path. Anat. u. Physiol. **207**:379, 1912.

24. May: Quoted by Naegeli.

25. Danchakoff, V.: Concerning the Conception of Potentialities in the Embryonic Cells, Anat. Rec. **10**:415, 1916.

The Origin of Blood Cells, Anat. Rec. **10**:397, 1916. The Wandering Cells in the Loose Connective Tissue of the Bird and Their Origin, Anat. Rec. **10**:483, 1916.

Naegeli,[2] Ehrlich,[26] Stockard,[27] Ziegler,[28] Türk,[29] Schriddé,[30] Fischer,[31] Butterfield, Stillman Meyer and Heinecke.[32]

Ehrlich[33] (1880) divided all white blood cells into granulated and nongranulated forms. It is this division which forms the basis of the modern dualistic teaching. He placed the lymphocytes, large mononuclears, and transitional cells among the nongranulated cells. The eosinophilic, basophilic and neutrophilic polymorphonuclears were the granulated cells. He believed the transitionals to be an intermediate form between the mononuclears and the neutrophils. Ehrlich believed that the lymphocytes came from lymphoid tissue, i. e., lymph node and spleen follicles, and that the granulocytes came from myeloid tissue, i. e., principally bone marrow. Today, this teaching, practically unchanged, is accepted by the dualists and the great majority of clinicians.

According to Naegeli's scheme the mesenchyme cell gives rise to the normoblast and this in turn to the normocyte. The mesenchyme cell also gives rise to the lymphocyte of the "quiet zone" of the follicle, this in turn to the "lymphoblast" of the germ center, and the "lymphoblast" gives rise to the small lymphocyte of the blood. The "myeloblast," the "stem cell" of the monocytes, megakaryocytes and polymorphonuclears, also comes originally from the mesenchyme cell. In postfetal life, therefore, all the blood cells come from their own specific "stem cells." He denies all transitions between the myeloid and lymphatic systems. He and other dualists meet the argument that myeloid metaplasia may occur in the spleen and lymph nodes in the absence of myeloid elements in the blood by declaring that lymph nodes and spleen are composed of two types of tissue, myeloid and lymphoid. The lymph node and spleen follicles are supposed to be

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26. Ehrlich, P., and Lazarus, A.: (Rewritten by A. Lazarus and O. Naegeli, and translated by H. Armit) Anemia, New York, Rebman Co., 1910, p. 148.

27. Stockard, C.: The Origin of Blood and Vascular Endothelium in Embryos Without a Circulation of the Blood and in the Normal Embryo, Am. J. Anat. **18**:227, 1915. A Study of Wandering Mesenchymal Cells on the Living Yolk Sac and Their Developmental Products; Chromatophores, Vascular Endothelium and Blood Cells, Am. J. Anat. **18**:525, 1915.

28. Ziegler, R.: Experimentelle u. klinische Untersuchungen über die Histogenese der myeloiden Leukämie, Jena, G. Fischer, 1906.

29. Türk, W.: Ueber Regeneration des Blutes unter normalen und krankhaften Verhältnissen, Centralbl. f. Allg. Path. u. Anat. **19**:895, 1908.

30. Schriddé, H.: Die embryonale Blutbildung. Erwiderung an Herrn Prof. A. Maximow, Zentralbl. f. Allg. Path. u. Anat. **20**:433, 1909.

31. Fischer, H.: Myeloische Metaplasie und fötale Blutbildung, Berlin, Julius Springer, 1910.

32. Butterfield, E. E., Heinecke, A., and Meyer, E.: Ueber das Vorkommen der Altmannschen Granulationen in den weissen Blutzellen, Folia haematol. **8**:325, 1909. Butterfield, E. E., and Stillman, R. G.: The Broader Aspects of Hematologic Diagnosis, Am. J. M. Sc. **154**:781 (Dec.) 1917.

33. Ehrlich, P.: Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes, Gesammelte mitteilungen, I Teil, 1891, Berlin.

lymphoid, while the interfollicular tissue of the nodes and splenic pulp are myeloid. They further claim that these two types of tissue are sharply contrasted and are distinct from each other. The myeloid function, however, does not manifest itself normally, but comes into play in anemias, infections, and myelogenous leukemias.

Schriddé [30] derives his lymphocytes from the endothelial lining of lymph vessels, and his myeloid tissue from the endothelial lining of blood vessels. This view, however, is untenable, because Thiel and Downey [34] have shown that in the spleen, where a large production of lymphocytes takes place, there are no lymph vessels.

Fig. 8.—Photograph of patient Feb. 17, 1919, seventy-two hours after roentgen-ray treatment of neck and face. See Figures 1 and 2.

Fischer,[31] a strong supporter of Naegeli's views, admits that myeloid cells may develop from endothelium of blood vessels and from connective tissue cells.

Hirschfeld [35] admits that the spleen and lymph nodes can produce granulocytes. They come, however, not from the specific follicular tissue but from the pulp and interfollicular tissue, probably from the perivascular tissue (Hirschfeld).

34. Thiel, G. A., and Downey, H.: The Development of the Mammalian Spleen, with Special Reference to Its Hematopoietic Activities, Am. J. Anat. **28**:279, 1921.

35. Hirschfeld, H.: Die Unitarische und die dualistische Auffassung über die Histopathologie der Leukämien, Folia haematol. **6**: 1, 1908.

Differential White Cell Counts on Twenty Successive Days on Which There Had Been Either a Distinct Rise or Fall in the White Count

	1 1/21/19	2 1/24/19	3 1/30/19	4 2/1/19	5 2/6/19	6 2/8/19	7 2/14/19	8 2/16/19	9 2/18/19	10 2/20/19	11 2/21/19	12 2/22/19	13 2/26/19	14 2/28/19	15 3/3/19	16 3/8/19	17 3/21/19	18 3/29/19	19 4/2/19	20 4/7/19
Polymorphonuclear neutrophils:																				
Percentage	3.2	85.6	7.8	26.75	4.66	4.4	3.6	5.33	9.25	1.4	2.8	6.5	1.8	4.25	0.4	19.33	33.66	6.0	1.83	1.4
Number	3,168	1,132.8	3,900	2,140	4,194	1,760	2,322	549	1,850	3,388	1,736	442	1,476	1,464	704	445	2,020—	14,820	9,150	9,044
Small lymphocytes:																				
Percentage	2.6	19.33	12.2	3.25	3.16	0.6	8.0	8.66	4.25	3.8	0.4	11.5	3.2	9.0	1.4	8.33	1.33	16.83	2.5	8.2
Number	2,574	928	6,100	260	2,844	240	5,160	892	850	9,196	248	782	2,624	3,078	2,464	192	80—	41,570	12,500	52,972
Large and medium lymphocytes:																				
Percentage	89.2	46.0	72.4	52.2	51.0	53.2	9.65	61.66	48.5	35.4	52.8	74.16	28.4	44.0	30.2	52.33	49.0	57.16	65.0	81.8
Number	88,308	2,167	36,200	4,180	45,891	21,280	6,227	6,349	9,700	85,668	32,736	5,044	23,288	15,049	53,152	1,204	2,940	142,420	325,000	528,428
Mononuclears:																				
Percentage	.....	.....	0.4	0.25	.....	.....	.....	.....	.....	.....	.....	.....	.....	0.5	1.8	.....	0.33	.....	0.16	
Number	.....	.....	200	20	.....	.....	.....	.....	.....	.....	.....	.....	.....	171	3,168	.....	20—	.....	800	
Transitionals:																				
Percentage	0.8	2.66	1.4	2.5	0.5	0.6	0.33	1.0	0.5	0.2	0.6	0.16	.....	0.75	0.2	2.0	.....	0.33	0.16	1.0
Number	792	127.7—	700	200	450	240	215	108	100	484	372	11—	.....	257	352	40	.....	815	800	5,400
Eosinophils:																				
Percentage	0.2	0.33	0.8	0.25	0.16	.....	0.5	.....	1.0	.....	.....	0.16	0.2	0.25	.....	.....	.....	0.66	0.16	
Number	198	16.2+	400	20	144	.....	323	.....	200	.....	.....	11—	164	86	.....	.....	.....	1,630	800	
Basophils:																				
Percentage	.....	0.33	0.4	0.75	0.16	.....	.....	0.33	.....	.....	.....	.....	.....	.....	.....	0.66	0.66	0.16	.....	0.2
Number	.....	16.2	200	60	144	.....	.....	33	.....	.....	.....	.....	.....	.....	.....	15+	40—	408	.....	1,292
Metamyelocytes:																				
Percentage	0.8	0.66	1.0	4.5	0.83	0.8	.....	0.33	0.25	0.2	0.6	0.16	0.4	1.25	.....	2.33	2.66	0.5	0.16	0.4
Number	792	31.7—	500	360	747	320	.....	33	50	484	372	11—	328	428	.....	54	160	1,285	800	2,584
Myelocytes:																				
Neutrophils—																				
Percentage	1.6	0.33	.....	2.75	0.5	0.2	0.66	.....	1.0	.....	0.2	0.33	0.2	2.25	0.2	3.0	0.33	0.66	0.5	0.8
Number	1,584	16.2	.....	220	450	80	426	.....	200	.....	124	22	164	770	352	60	20—	1,630	2,500	5,168
Eosinophils—																				
Percentage	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	0.2	.....	.....	.....	.....	.....	0.16	
Number	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	164	.....	.....	.....	.....	.....	800	
Basophils—																				
Percentage	0.2	.....	.....	.....	.....	.....	.....	.....	.....	.....	0.6	0.16	.....	.....	0.2	0.33				
Number	198	.....	.....	.....	.....	.....	.....	.....	.....	.....	372	11—	.....	.....	352	8—				
Micromyeloblasts: lymphoidocytes: or stem cells:																				
Percentage	1.4	5.66	1.8	6.75	17.66	5.4	49.0	6.0	20.75	40.0	13.0	0.16	55.6	19.0	28.6	6.66	1.66	13.16	15.16	0.4
Number	1,386	271.7	900	540	15,894	2,160	31,605	618	4,150	96,800	8,060	11—	45,592	6,498	50,336	158	100	32,505	75,800	2,584
Mitotic figures:																				
Percentage	.....	.....	.....	.....	0.66	0.2	.....	.....	.....	.....	0.6	.....	0.4	.....	.....	.....	.....	.....	0.5	0.4
Number	.....	.....	.....	.....	594	80	.....	.....	.....	.....	372	.....	328	.....	.....	.....	.....	.....	2,500	25,840
Degenerated cells:																				
Percentage	0.2	1.0	1.0	.....	20.5	34.6	28.16	16.66	.....	19.0	28.4	5.66	0.6	18.75	37.0	5.0	10.33	4.5	13.66	5.4
Number	198	48	900	.....	18,450	13,840	18,163	1,716—	.....	45,980	15,608	385—	7,872	6,412	65,120	115	620	11,115	68,300	34,884
No. of cells counted:																				
Percentage	100.0	99.96	100.0	100.0	99.94	100.0	.....	99.97	100.0	.....	100.0	99.95	100.0	100.0	100.0	99.97	99.99	99.96	99.96	100.0
Number	500	300	500	400	600	500	.....	300	400	.....	500	600	500	400	500	300	300	600	600	500
Nucleated R. B. C.:																				
Percentage	3.0	0.66	1.4	1.25	0.16	0.6	.....	.....	1.25	0.4	0.6	0.5	1.2	1.5	1.2	1.66	0.66	1.0	.....	0.6
Number	2,970	79.6	700	100	144	240	322	.....	250	968	372	34	984	513	2,112	38	40	2,470	.....	3,876
Total W. B. C. count	99,000	4,800	50,000	8,000	90,000	40,000	64,500	10,300	20,000	42,000	62,000	6,800	82,000	34,200	176,000	2,300	6,000	247,000	500,000	646,000

Stockard [16] adopts the extreme polyphyletic view. The fixed mesenchymal cells of the embryonic body, even before they begin their migration are already specialized to such an extent that differentiation can take place in one direction only.

Pappenheim and his pupils [14] hold a moderated monophyletic view. The "histioidocyte" a tissue cell gives rise to the "lymphoidocyte." The lymphoidocyte is the only stem cell and gives rise to megakaryocytes, monocytes, polymorphonuclears, lymphocytes and red blood cells. The lymphocytes are fully differentiated cells and can not change into granulocytes.

Ferrata,[20] and his pupil Neigreiros-Rinaldi, accept a modified monophyletic view, similar to the one proposed by Pappenheim. They believe that all the blood cells come from a single stem cell, which they call the "hemocytoblast," they do not believe that fully differentiated lymphocytes are capable of differentiating into granulocytes or red blood cells.

Ferrata considers the connective tissue as a diffuse hemopoietic organ. This tissue gives rise to the "hemohistioblast" (resting-wandering cells of Maximow; clasmatocyte of Ranvier [36]). In the early embryo this cell differentiates into the primitive transitory hemocytoblast, and this, in turn, to the primitive red blood cell of the embryo (megalocytes); while in the adult, lymphoid and myeloid hemocytoblasts (functional differences only) and monocytes are the products of its differentiation.

Grawitz,[16] Weidenreich,[17] Danchakoff,[25] and Maximow,[18] hold the extreme monophyletic view. They believe that all blood cells may come from fixed tissue cells, such as reticular cells, fixed cells of omentum and messentery, as well as from the widely distributed clasmatocytes. These may give rise to free lymphoid cells, and these lymphoid cells may occur anywheres in the body of the adult.

Fully differentiated lymphocytes derived from these lymphoid cells may, according to some authors, dedifferentiate into the more primitive type of lymphoid cell, which, in turn, might differentiate into other forms of white cells, or these fully differentiated lymphocytes might metamorphose into other forms of leukocytes without dedifferentiation. Grawitz believes that lymphocytes can change into granulocytes in the circulating blood.

Weidenreich [17] and Downey [19] do not recognize the term "lymphoblast." They have shown that all the types of lymphocytes are concerned in regeneration and differentiation from one type to another. The reticulum of lymphoid tissue, wherever found, serves as a mother tissue. All types of lymphocytes may be derived from it, and these,

36. Ranvier, L.: Des Clasmatocytes, Arch. d'Anat. micr. **3**:122, 1900.

in turn, may become transformed into other types of lymphocytes. Therefore, no one type of lymphocyte can be recognized as being more highly differentiated than any other type. They claim, therefore, that one cannot speak of a "stem cell" of the lymphocyte in the same sense that one can speak of the "stem cell" of the myeloid cells.

Lymphocytes are not in any sense of the word a final product. Downey,[19] Weill,[37] Weidenreich,[17] and other observers have shown that all forms of lymphocytes can differentiate specific leukocyte granules, thereby becoming granular leukocytes.

Such widely differing opinions indicate the unsettled state of many hematologic questions. These questions regarding the relationship of the blood cells depend primarily on the various theories of postfetal regeneration. Is Naegeli [38] correct, for instance, in assuming that the "myeloblast" is a specific myeloid cell which is in no way related to the lymphatic tissues? He claims that he can differentiate morphologically between the myeloblast and large lymphocyte (lymphoblast). Pappenheim [14] claims that Naegeli's myeloblast is not a stem cell but is the cell which he terms the leukoblast, a cell already partly differentiated along myeloid lines.

The following points are usually considered by the dualists as differentiating between "myeloblasts" and "lymphoblasts."

1. *Character of Chromatin Arrangement.*—Naegeli [39] (1907) describes very poor chromatin content as characteristic for lymphoblasts. Klein [40] (1910) finds that the chromatin content is not characteristic of the cell. He shows lymphoblasts which are identical with du Toit's [21] and Pappenheim's lymphoidocytes and with Naegeli's myeloblasts.

2. *Number of Nucleoli.*—Naegeli (1907) claimed that nucleoli of the "lymphoblasts" are one or two in number, and of myeloblasts from two to four in number. Pappenheim,[41] Klein,[41] Butterfield [42] and others have shown that this is not true. Naegeli himself admitted later [2] (1912 and 1919) that this does not hold true in pathologic blood.

3. *Altmann-Schriddé Granules.*—The dualists believed that they occurred in lymphoid cells and were absent in myeloid cells. Türk

37. Weill, P.: Ueber die Bildung von Leukozyten in der Menschlichen und tierischen Thymus des erwachsenen Organismus, Arch. f. mikro. Anat. **83**:305, 1913.

38. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Leipzig, 1919, Dritte auflage.

39. Naegeli: Quoted by Du Toit.

40. Klein: Ueber die groszen einkernigen Leukozyten des Leukämieblutes, Folia haematol. **10**: 1, 1019.

41. Pappenheim and Klein: Quoted by Du Toit.

42. Butterfield: Quoted by Damarus.

(1912)[43] has shown that these granules are not specific for lymphoid cells.

4. *Oxydase Reaction.*—The dualists claim that the oxydase reaction, the staining of the oxydase grandules with the indophenol blue dye, is positive in myeloblasts and negative in lymphoblasts.

Hyneke,[44] Decastello,[45] Blühdorn, Jochman,[46] Glaus[47] and Dunn[48] report cases in which the so-called "myeloblasts" did not give the oxydase reaction. Klein[49] showed that ordinary lymphocytes may give a positive reaction.

Schultze[50] found that the myeloblasts of the normal marrow usually did not give the reaction while the pathologic myeloblasts in the blood and in the organs usually do give the reaction.

According to Menten[51] the reaction is not specific for myeloid cells. She found that lymphocytes may give a well marked reaction. She also found that all tissues with the exception of bone give this reaction, so that it is by no means specific for blood cells.

Forman and Hugger[52] found "large mononuclears" both with and without the indophenol oxydase granules.

Boéchat,[53] Belz,[54] Steffan[55] and Krjukow[3] claim that the reaction may be absent in myeloblasts.

Naegeli himself wavers on the question of the specificity of the oxydase reaction. In his book[38] (p. 211) he makes the statement "the oxydase reaction is present in normal myeloblasts and generally in pathologic myeloblasts, but in some of these the reaction may be not so strong and less diffuse."

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43. Türk, W.: Vorlesungen über klinische Haematologie, Wien. u. Leipzig. W. Braumüller, 1912, Pt. 2, p. 131.

44. Hyneke, K.: Zur Monocytenfrage, Folia haematol. **13**:345, 1912.

45. Decastello: Quoted by Hyneke.

46. Jochman and Blühdorn: Ueber akute Myeloblasten Leukämie, Folia haematol. **12**:1, 1911.

47. Glaus: Quoted by Kahle, H.: Ueber ein Hämogonien und Leukozyten erzeugendes Angiosarkom in zirrhotischer Leber, Arch. f. path. Anat. u. Physiol. **226**:44, 1919.

48. Dunn, J. S.: The Use of the Oxydase Reaction in the Differentiation of Acute Leukemias, Quart. J. M. **6**:293, 1913.

49. Klein: Quoted by Neumann.

50. Schultze, W. H.: Zur Differentialdiagnose der Leukämieen, München. med. Wchnschr. **56**:167, 1909.

51. Menten, M. L.: A Study of the Oxydase Reaction with *a*-naphtha-paraphenyldiamene, J. M. Res. **40**:433, 1919.

52. Forman, J., and Hugger, C. C.: Nature of Mononuclear Cells Seen in Exudate of Lobar Pneumonia Accompanying Typhoid Fever, Am. J. M. Sc. **155**: 317 (March) 1918.

53. Boéchat: Ueber akute Myeloblastenleukämie mit teilweise chloromatösen Charakter, Frankf. Ztschr. f. Path. **13**:489, 1913.

54. Belz, L.: Ueber Leukämie mit besonderer Berücksichtigung der Akuten Form, Deutsch. Arch. f. klin. Med. **113**:116, 1914.

55. Steffan, M.: Ueber einen Fall akuten Myeloblasten Leukämie und über die Beziehungen Leukämie-Sepsis, Folia haematol. **21**:59, 1916.

Pappenheim and Döhrer's [56] conclusion regarding the oxydase reaction is, that it does not indicate an absolute unfailing histogenetic difference between two heterogenous cell races. It is clear, therefore, that the opinion of many of the observers is against the specificity of the oxydase reaction and against any of the other differential points usually picked on by the dualists for the differentiation of lymphoblasts and myeloblasts.

Du Toit [21] says that morphologically we cannot differentiate between "lymphoblasts" and "myeloblasts."

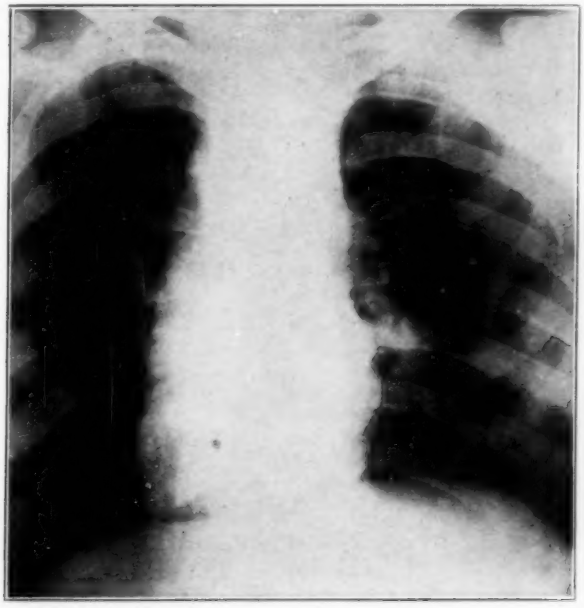

Fig. 9.—Roentgenogram of chest, Jan. 21, 1919.

Krjukow,[8] referring to his case of microlymphoidocytic leukemia, says: "It seems to me that the most skilful dualists could not possibly differentiate our microlymphoidocytes from true micromyeloblasts, except, perhaps, by the use of the various methods that the dualists are wont to use."

Hirschfeld [57] could not see any morphologic difference between myeloblasts and germ center cells.

56. Döhrer and Pappenheim, A.: Ein weiterer Fall von akuten Mikrolymphoidozyten leukämie, Folia haematol. **16**:143, 1913.

57. Hirschfeld, H.: Die Unitarische und die Dualistische Auffassung über die Histopathologie der Leukämien, Folia haematol. **6**:382, 1908.

Damarus,[58] Wolf and Türk [59] and Butterfield [60] can see no morphologic difference between the stem cells of lymphocytes and granulocytes.

Weber [61] describes a case of leukemia in which "the conclusion was unavoidable that the lymphoid cells which permeated the various tissues of the body were of the same kind as the lymphoid cells which during the patient's life constituted by far the greatest portion of the white cells of his circulating blood. I thought at the time that the cells in question were probably to be regarded as lymphoblasts but

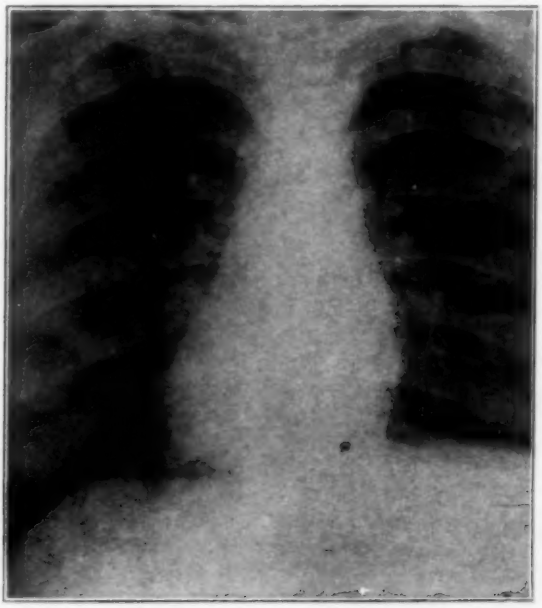

Fig. 10.—Roentgenogram of chest, Jan. 31, 1919, ten days after roentgen-ray treatment of mediastinum. Compare with Figure 9.

from the fact that a few of the cells gave a positive oxydase reaction and from a comparison with Case 4, I now think that they were probably myeloblasts."

58. Damarus: Der gegenwärtige Stand der Leukämiefrage, Folia haematol. **6**:337, 1908.

59. Wolf and Türk: Quoted by Damarus.

60. Butterfield, E. E.: Ueber die ungranulierten Vorstufen der Myelocyten und ihre Bildung in Milz, Leber und Lymphdrüsen, Deutsch. Arch. f. klin. Med. **92**:336, 1903.

61. Weber, F. P.: Acute Leukemia and So-Called Mediastinal Leukosarcomatosis (Sternberg), with the Account of a Case Accompanied by Myeloid Substitution of the Hilus Fat of the Kidneys, Quart. J. M. **12**:212 (April) 1919.

Similarly Chosrojeff [62] reports a case of "micromyeloblastic leukemia" in which he found in the blood all transition forms from myeloblasts to small lymphocytes and "were it not for the oxydase reaction, one could not tell what type of leukemia he was dealing with."

Walter Schultze,[50] a dualist, admits that the morphologic differences between myeloblasts and lymphoblasts, described by Schriddé, are so slight that the majority of hematologists cannot differentiate the two types of cells.

We have shown so far that "lymphoblasts" cannot be differentiated from "myeloblasts" either by morphology, that is cytoplasm, nuclear chromatin arrangement, nucleolar content, Altmann-Schriddé granules,

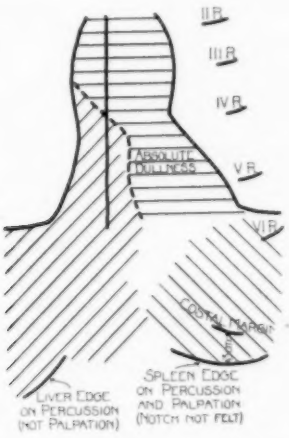

Fig. 11.—Percussion tracing January 27, showing diminution in size of mediastinal dulness. Compare with Figure 3.

or by the oxydase reaction. The dualists trace all the white blood cells from these two stem cells and claim that the lymphopoietic and myelopoietic tissues derived from these two mother cells are entirely distinct, and that lymphoid tissue cannot produce myeloid cells and, vice versa, that myeloid tissue cannot produce lymphoid cells. In the presence of a vast amount of recently accumulated evidence to the contrary, both experimental and clinical, it becomes doubtful whether there exists such a cell as is usually described by the dualists as a "lymphoblast."

The following points are evidence against the dualistic and polyphyletic theories.

62. Chosrojeff, B. P.: Myelosis aleucemica acuta micromyeloblastica, Folia haematol. **20**:33, 1915.

1. Downey and Weidenreich have demonstrated that cells such as are described for the germ centers may be found in the interfollicular tissue, in the spleen pulp, and in the lymph vessels. They have also shown that morphologically and genetically the lymphocytes of the cortex and medulla of lymph nodes are identical, and that follicles with germ centers may arise anywheres in the node.

2. Weidenreich describes these same cells in the chyle of the thoracic duct.

3. Dominici has shown that in certain infections, in man and in the laboratory animals, neutrophilic and eosinophilic myelocytes and normoblasts may develop in the spleen and lymph nodes from lymphocytes.

4. Sacerdotti [63] and Frattin, by tying off and cutting the blood vessels of one kidney in dogs have produced true bone and bone marrow in the pelvis of the kidney.

5. Maximow [64] reproduced these same results and found that these granulated and red blood cells of the bone marrow came from typical lymphocytes of the blood.

6. Downey and Weidenreich [19] have shown that the lymphocytes of the germ center are extremely irregular in size and form and that only a very few of them conform to the descriptions given by Naegeli, Türk, Pappenheim and others.

7. Naegeli himself at one time (1900) describes the lymphoblasts as being very rich in chromatin and at another time (1909) as being very poor in chromatin. They are very young lymphocytes related to the mature lymphocytes by innumerable transition forms. In children they may be found at times in normal blood, and are especially prone to occur in infectious leukocytoses (Naegeli [65]).

8. Weidenreich and Weill [37] claim that lymphocytes may differentiate into neutrophil and eosinophil leukocytes.

9. Downey [66] has shown that lymphocytes may differentiate into histogenous mast cells. Weidenreich and Downey [19] have shown granulated myelocytes developing from the lymphocytes of the spleen. They have also shown granulated cells in mitosis in the spleen.

10. Dominici [67] has observed myelocytes in lymph follicles.

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63. Sacerdotti, C., and Frattin, G.: Ueber die heteroplastische Knochenbildung, Virchows Arch. f. path. Anat. **168**:431, 1902.

64. Maximow, A.: Experimentelle Untersuchungen zur postfötalen Histogenese des myeloiden Gewebes, Beitr. z. path. Anat. u. z. allg. Path. **41**:122, 1907.

65. Naegeli: Blutkrankheiten und Blutdiagnostik, Leipzig, 1919.

66. Downey, H.: The Development of the Histogenous Mast Cells of Adult Guinea-Pigs and the Structure of the Histogenous Mast Cell of Man, Folia haematol. **16**:70, 1913.

67. Dominici: Quoted by Hirschfeld.[37]

11. In a case of eosinophilic polymorphonuclear hyperleukocytosis recently reported by Giffin,[68] Downey has found eosinophilic myelocytes in the germ centers of the follicles of the lymph nodes and spleen.[69]

12. Hertz,[70] using pyrogallol, has produced myeloid metaplasia of the spleen pulp with a hyperplasia of the splenic follicles. This is contrary to the usual statement that myeloid metaplasia is accompanied by reduction in the size of the follicles, which is used as an argument in favor of the supposed antagonism between pulp and follicles.

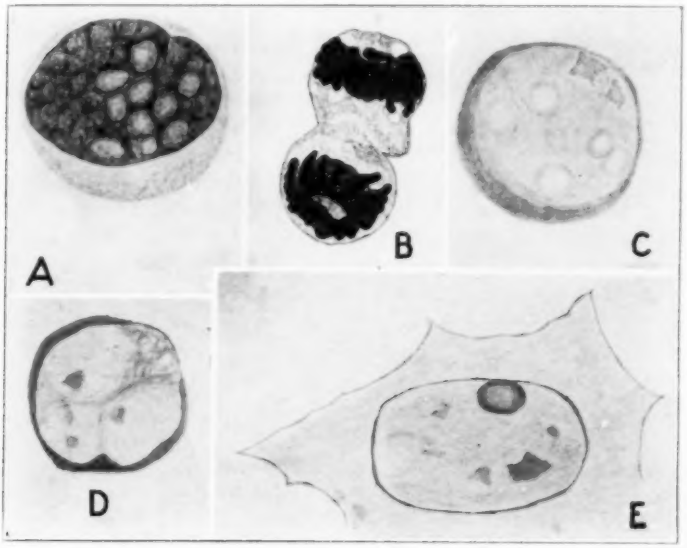

Fig. 12.—The cells in A and B are drawn with 1.9 mm. objective and No. 8 eyepiece; magnified ×2 actual appearance. A. Microlymphoidocyte (stem cell) (micromyeloblast) in blood. B. White cell in mitosis in blood stream. C. Microlymphoidocyte or stem cell in section. Objective 1.5 mm.; ocular No. 8; magnification ×8. D. Stem cell or microlymphoidocyte in section. Objective, 1.5 mm.; ocular, No. 8; magnification, ×8. E. Reticulum cell in section. Objective, 1.5 mm.; ocular, No. 8; magnification, ×8.

13. Downey has demonstrated eosinophilic myelocytes in the germinal centers of lymph nodes of rabbits, the subjects of experimental hemorrhages in which there were no myelocytes in the blood so that the development of these myelocytes must have taken place in loco.

68. Giffin, H. Z.: Persistent Eosinophilia with Hyperleukocytosis and Splenomegaly. Am. J. Med. Sc. **158**:618, 1919.

69. Unpublished observation.

70. Hertz: Quoted by Krjukow.[3]

14. Roman[71] has observed germ centers containing myelocytes.

I have attempted to bring out the following points.

1. Hematologists are divided into two main camps—the dualists, or polyphyletists, and the unitarians.

2. The dualists and polyphyletists believe that the blood cells and blood forming organs are divided into two main distinct divisions, the myeloid and lymphoid. These two never change from one into the other either in the tissues or in the blood.

3. The unitarians believe that all blood cells come from the "lymphocyte" found in the bone marrow, spleen, lymph nodes and other tissues of the body, or, according to Pappenheim and his followers, from the "lymphoidocyte," which, in the adult, is confined to the marrow.

4. The dualists claim that they can differentiate between the "lymphoblast" and "myeloblast." They regard the oxydase reaction as being of prime importance for such differentiation.

5. The unitarians claim that such a differentiation is impossible; that the "lymphoblast" as a cell per se does not exist; that the "lymphoblast" is given various descriptions by various authors; that Naegeli himself makes contradictory statements regarding this cell; that the "lymphoblast" may be found anywhere in lymphoid tissue and not only in the germinal centers, as claimed by the dualists, and that the oxydase reaction, the main stay of the dualists, is not a specific test for the myeloblast.

6. A vast amount of experimental evidence is accumulating, which is in favor of the unitarian theory.

We now wish to call attention to histologic and hematologic evidence in which we consider to be in favor of the unitarian theory, reported to date in the literature on leukemia.

Dr. Downey has been kind enough to permit me to study the blood from a recent case of leukemia in which all the transition stages between the lymphoidocyte (myeloblast of Naegeli) and lymphocyte were present.[72]

Fleischmann[73] reports a case of monocyte leukemia (second case on record) in which in June, 1913, he found 65 per cent. mononuclear leukocytes and 19 per cent. small and large lymphocytes. In November, 1913, a bone marrow puncture gave polymorphonuclears, small lymphocytes and "mononuclears" identical in morphology with those found in the blood. Shortly before death, the "mononuclears" dropped

71. Roman, B.: Zur Kenntniss der myeloischen Chloroleukämie, Beitr. z path. Anat. u. z. allg. Path. **55**:61, 1913.

72. This case is not yet reported in the literature.

73. Fleischmann, P.: Der zweite Fall von Monocyten leukämie, Folia haematol. **20**:17, 1915.

to 25 per cent. and there appeared, in the blood, myelocytes, 12½ per cent., promyelocytes and "myeloblasts." At the necropsy there was found myeloid change everywhere. Among the myeloid cells were cells which corresponded to the blood monocytes. The follicles were shrunken in the spleen and the lymph nodes. Fleischmann concludes the report by suggesting the possibility that the monocytes changed into myeloid elements under the influence of some pathologic stimulus.

Pappenheim,[74] Walz,[75] and Dennig[76] have reported cases which hematologically were cases of lymphatic leukemia. Yet, in these cases

Fig. 13.—Axillary lymph node ×8, showing one distinct follicle with a germinal center.

the spleen and lymph nodes were not involved, but the bone marrow had become lymphoid.

Krjukow[3] (1915) reports a case of microlymphoidocytic leukemia in which the blood showed all transition forms from the stem cell to the mature granulocyte, yet the pathologico-histologic changes were

74. Pappenheim, A.: Ueber Lymphämie ohne Lymphdrüsenschwellung. Ztschr. f. klin. Med. **39**:171, 1900.

75. Walz: Quoted by Damarus.

76. Dennig, A.: Ueber akute Leukämie, München. med. Wchnschr. **47**: 1297, 1900.

those of a lymphatic leukemia. The bone marrow showed only slight activity. The pulp of the spleen and some lymph nodes showed slight myeloid metaplasia. The thymus was hyperplastic and the spleen and lymph nodes showed typical lymphatic leukemia changes. He concludes that the myeloid elements of the blood were coming from the lymph nodes and spleen. He also states that the most skilful dualist could not differentiate morphologically between micromyeloblasts and his microlymphoidocytes. He is loath to conclude from this that the myeloid cells of the blood were coming from lymphoid cells and so decides that he has here a case of "mixed leukemia," with a prevailing "lymphatic component." He also concludes that in acute leukemias even the presence in the blood of myelocytes and promyelocytes and stem cells does not necessarily diagnosticate a myelogenous leukemia.

St. Klein [77] (1910) reports a case in which the blood showed all the transition stages between the lymphoidocyte (myeloblast) and the ordinary lymphocyte. The histologic studies showed a lympholeukemic involvement of all the lymphoid tissues.

Türk [78] reports a case of mixed cell leukemia which changed into a lymphatic leukemia.

Hirschfeld [57] has found in cases of mixed cell leukemia hyperplasia of the lymph follicles and a myeloid metaplasia in the rest of the lymph nodes. He has also found in a true case of lymphatic leukemia clumps of myelocytes in the spleen and lymph nodes.

Veszpremi,[79] Glinski,[80] Walter Schultze, Pappenheim,[81] Hirschfeld [82] and Wechselmann describe cases of acute lymphatic leukemia in which there was no proliferation or atrophy of the follicles of the spleen or of the lymph nodes or of both with marked proliferation of the splenic pulp and interfollicular tissues in some of the cases. Hematologically these cases were the same as any ordinary acute lymphatic leukemia, yet histologically we find the proliferation where it should occur in myeloid cases (Hirschfeld [57]).

Hertz [83] (1909) reports a case of lymphatic leukemia in which 15 per cent. of myelocytes appeared before death. Sections of lymph nodes showed lymphatic proliferation as well as neutrophilic granulated

77. St. Klein: Quoted by Du Toit.

78. Türk: Quoted by Hirschfeld.[57]

79. Veszpremi, D.: Beitrage zur Histologie der sogenannten "akuten Leukämie," Arch. f. path. Anat. u. Physiol. **184**:220, 1906.

80. Glinski, L. K.: Zur pathologischen Anatomie der akuten Lymphämie. Arch. f. path. Anat. u. Physiol. **171**:101, 1903.

81. Schultze and Pappenheim: Quoted by Hirschfeld.

82. Wechselmann, W., and Hirschfeld, H.: Ueber einen Fall akuter myeloider makrolymphozytärer Leukämie mit eigentümlichen Zelleinschlüssen. Ztschr. f. klin. Med. **66**:349, 1908.

83. Hertz, A.: Zur Frage der gemischten Leukämie. Wien. klin. Wchnschr. **22**:1030, 1909.

myelocytes and erythrocytes. In the bone marrow, follicle like aggregations of lymphocytes were present, besides the myelocytes and myeloblasts. The spleen pulp was myeloid, while the follicles were atrophied.

Chosrojeff [62] (1915) reports a case of "micromyeloblastic" leukemia in which the blood showed all transition forms between the "myelo-

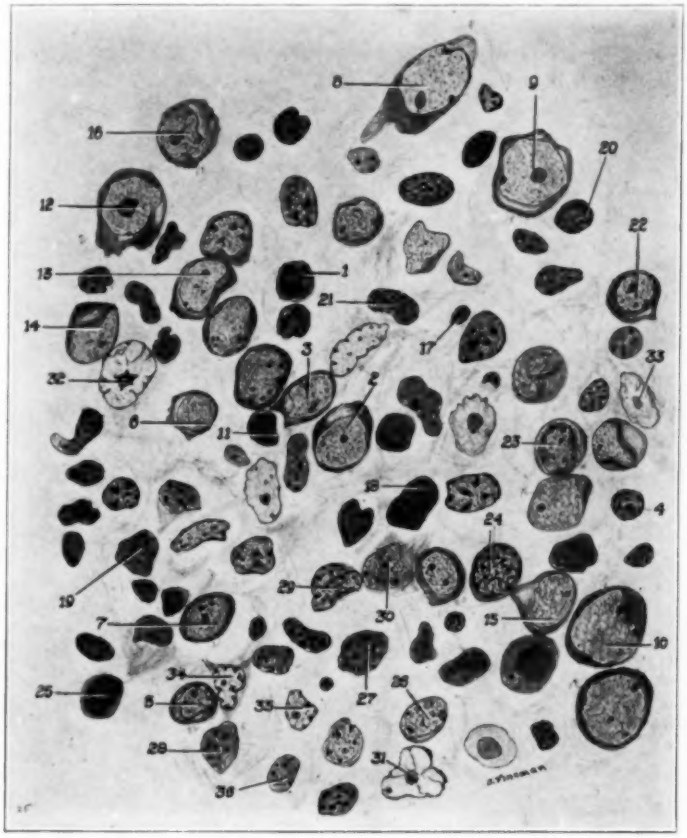

Fig. 14.—Germ center of follicle shown in Figure 13. Objective: Zeiss apochromatic 1.5 mm.; ocular, Zeiss compensating No. 8. Note the numerous stem cells in this germ center.

blast" and the small lymphocyte. He bases his diagnosis on a positive oxydase reaction and says, "were it not for this reaction one could not tell what type of leukemia he was dealing with."

Herxheimer[84] (1913) reports a case of mixed leukemia. The blood contained 69.8 per cent. small lymphocytes and 25.4 per cent. "myeloblasts." The bone marrow showed mostly lymphocytes with a few islands of "myeloblasts." The spleen showed a hyperplasia of follicles, which consisted of large and small lymphocytes. The pulp showed a hyperplasia of its lymphoid constituents and a profuse scattering of "myeloblasts." The lymph nodes showed a hyperplasia of follicles and occasional "myeloblasts." In the bronchial nodes the "myelob'asts" predominated. The mediastinum showed compact parts consisting largely of lymphocytes and loose areas containing many "myeloblasts." The "myeloblasts" were diagnosed by means of the oxydase reaction.

The author regards this positive oxydase reaction as the best indication of the dualistic origin of the myeloid and lymphoid cells.

From these cases the following is evident:

1. The blood may show all transition forms from the "myelob'ast" (lymphoidocyte) to the ordinary lymphocyte (Downey).

2. A monocytic leukemia blood and bone marrow picture changed to a myeloid picture (Fleischmann). The necropsy showed myeloid proliferation everywhere. Among the myeloid cells some monocytes were present.

3. The blood picture was one of lymphatic leukemia (Pappenheim and others). The bone marrow had undergone a lymphoid change and nodes and spleen were normal.

4. The blood showed all transition forms from the "micromyeloblast" to the granulocyte (Krjukow). These "micromyeloblasts" were coming from lymphoid tissue, "from the myeloid parts of these organs."

5. The blood showed all transition stages between the "myeloblast" and the ordinary lymphocyte (Klein). The tissues showed only lymphoid proliferation.

6. A mixed cell leukemia changed into a lymphatic leukemia (Türk).

7. Clumps of myelocytes were present in the spleen and lymph nodes in a case of lymphatic leukemia (Hirschfeld). In a case of mixed cell leukemia, both myeloid and lymphoid proliferation were present in the lymph nodes.

8. Cases of acute lymphatic leukemia showed atrophy of the follicles of the spleen or of the lymph nodes or of both, and a proliferation of the interfollicular tissue and spleen pulp in some of the cases, tissue which according to the dualists is myeloid in nature (Veszpremi and others).

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84. Herxheimer, G.: Ueber einen combinierten Fall von Lymphätischer und Myeloblastenleukämie, Zentralbl. f. allg. Path. **24**:897, 1913.

9. A case of lymphatic leukemia in which numerous myelocytes appeared before death (Hertz). The bone marrow showed lymphocytes in follicle arrangement and the spleen pulp showed myeloid proliferation with atrophy of the follicles.

10. In the blood all transition forms from the "myeloblast" to the lymphocyte were present (Chosrojeff). The diagnosis of "myeloblast" is made on the strength of the oxydase reaction.

11. In a case of mixed leukemia (Herxheimer) the bone marrow showed mostly lymphocytes with a small number of "myeloblasts." The spleen, lymph nodes and mediastinal tumor showed hyperplasia of lymphoid and myeloid cells. Here, too, the diagnosis of "myeloblast" was based on the oxydase reaction.

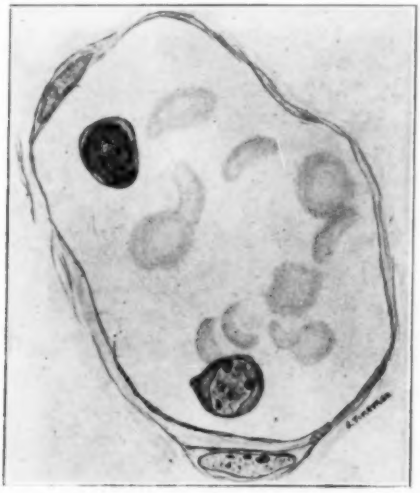

Fig. 15.—Small blood vessel in the lymph node, showing in the lumen a lymphocyte above and typical stem cell below. Objective Zeiss 1.5 mm., apochromatic; ocuar, Zeiss No. 8 compensating.

All of the above evidence is more or less of an indirect nature.

Meyer, Heinecke, Ziegler, Naegeli and other dualists claim a biologic antagonism between the follicles and interfollicular tissues. They claim that no one has ever observed myeloid tissue in the germinal centers of the spleen or lymph nodes.

In 1912, Pappenheim [85] made the statement that the unitarian theory will receive great support, and Lydtin,[86] in 1913, declared that the

85. Pappenheim, A.: Bemerkungen zur Frage der akuten Myeloblastenleukämie und Leukosarcomatose, Wien. klin. Wchnschr. **25**:163, 1912.

86. Lydtin, H.: Ein Fall von Micromyeloblasten leukämie, Folia haematol. **15**:316, 1913.

dualistic theory will receive a serious blow at the moment that a case would be found in which the so-called "myeloblasts" could be shown to originate from lymphatic tissue, that is, from the follicles and follicular cords. In other words, when in the blood the cell morphology will be that of a "myeloblastic" leukemia, while the tissues will show lympholeukemic changes, i. e., follicular hypertrophy and presence of myeloblasts within the lymph follicles.

Hirschfeld (1908) says that so far researches have shown that although the spleen and lymph nodes can produce granulocytes, yet they come not from the specific follicular tissue but from the pulp and interfollicular tissue.

Naegeli (1910) makes the statement that under no circumstances has it ever been proven that the germinal center of the lymph nodes can act as the site of origin of myeloid cells.

In 1915, Citron published his case of which he says, "It is the only one to date which shows in a seemingly certain and irreproachable manner, that the dualistic division does not always hold true; that not in all cases in which a myeloid metaplasia takes place is it necessary to conclude that a substitution of the lymphatic tissue has taken place by extra parenchymatous myeloid tissue; that in some cases a direct autocellular change of lymphatic follicular lymphocytes into myeloid cells may take place. Citron bases this statement on the following findings.

1. The blood showed a monotonously uniform picture of the so-called "myeloblasts" of Naegeli or "lymphoidocytes" of Pappenheim.

2. The bone marrow was normal.

3. In the lumina of the blood vessels of the spleen and lymph nodes the cells were exactly the same as those which permeated these organs.

4. The splenic pulp and interfollicular tissue of the lymph nodes consisted of cells similar in all respects to the cells of which the follicles were composed.

5. No signs of follicular atrophy were present.

6. No evidence of myeloid metaplasia of the interfollicular tissue was present.

7. The nuclei of the cells of the follicles and of the interfollicular tissue were not those of lymphocytes but of "myeloblasts."

8. These "myeloblasts" could be seen entering the circulation from the hyperplastic lymph follicles.

HEMATOLOGIC AND HISTOLOGIC FINDINGS

A. Blood.—The differential counts are shown in Table 4. The various interesting findings of the blood have already been referred to

in the clinical discussion of the case. I wish again, however, to call attention to the presence of numerous "stem cells" (lymphoidocyte of Pappenheim; myeloblast of Naegeli). These cells were present in the blood during the entire stay of the patient in the hospital. They were extremely variable in size. Some were as large as a large lymphocyte, others were smaller than a red blood cell. In the differential counts we included all sizes under the headings "lymphoidocytes," "myeloblasts," "micromyeloblasts" or "stem cells." As seen in smears stained in Wright's stain, the cells (Fig. 12A) are morphologically identical with those described by Pappenheim. Their cytoplasm is basophilic, and scant in amount. The majority of cells did not contain

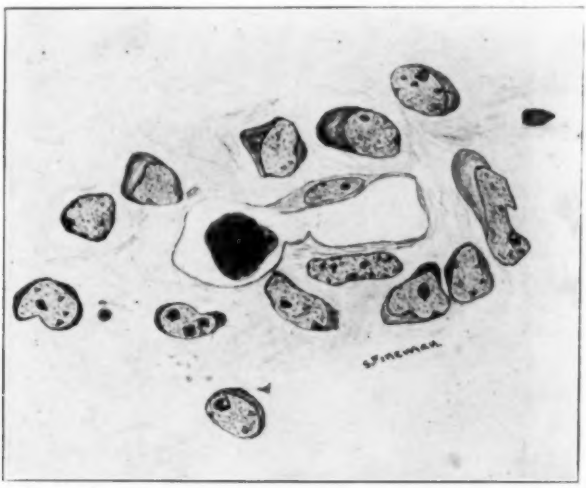

Fig. 16.—Portion of lymph node capsule. Stem cells in majority. Mitotic figure in a small blood vessel. Cell 1, forming part of vessel wall, is an endothelial cell. Cell 2, immediately below, is a connective tissue cell. Objective 1.5 mm., Zeiss apochromatic; ocular No. 8, compensating, Zeiss.

azure granules. The structure of the nuclei forms the diagnostic feature of these cells. The chromatin forms a very fine, evenly distributed sievelike meshwork, in contrast to the large clumped chromatin blocks which characterize the nucleus of the lymphocyte. Nucleoli, in variable numbers, are usually present. The staining of the chromatin sievelike network of the stem cell is much lighter than that of a lymphocyte. With the slightest overstaining the typical appearance of the stem cell becomes altered and differentiation from the lympocyte is difficult.

The oxydase reaction was positive in the polymorphonuclear leukocytes but negative in all other cells. As already pointed out, the

failure of the stem cells to show the oxydase granules is of no significance one way or another. Citron and others refer to cases unquestionably myeloid in character in which this reaction was negative.

Naegeli (1912 and 1919) wavers on the specificity of the oxydase reaction. He says that the oxydase reaction is positive in normal myeloblasts and for the most part in pathologic myeloblasts.

Hyneke, Decastello, Dunn, Jochman and Blühdorn declare that the oxydase reaction need not be positive in unripe myeloid cells.

Boéchat and Belz claim that the reaction may be absent.

Klein has shown that even lymphocytes may give a positive oxydase reaction.

Menten has shown that lymphocytes and many tissues give a positive reaction, so that the reaction is not only not specific for myeloid cells, but is not even specific for blood cells.

Morphologically, the cells in our case were identical with those the dualists call "myeloblasts" and "micromyeloblasts." If the blood alone were examined, the diagnosis from the dualists' point of view would be acute micromyeloblastic leukemia. I will endeavor to show that these "micromyeloblasts," probably the majority of them, certainly a great many of them, were coming from the follicles and germinal centers of the lymph nodes.

In the blood numerous transition forms between these "micromyeloblasts" and lymphocytes were found. I have already pointed out that the slightest overstaining alters the appearance of these cells. Transition forms, however, were found in well stained smears, side by side with the typical "micromyeloblasts." I believe that these transition forms are another bit of evidence showing the relation of "micromyeloblasts" to lymphopoietic tissues.

The number of the "micromyeloblasts" varied roughly with the total white cell count. Table 4 shows these variations. Figure 4 shows three curves expressing the relation between the total white count, the total "micromyeloblast count" and the relative percentage of these cells. The rise in total number of these "micromyeloblasts" was invariably associated with an exaggeration of all clinical symptoms, and an enlargement of either the spleen, lymph nodes or tonsils. It would appear, therefore, that the increase of these cells in the circulation was closely associated with the increased activity of the lymphopoietic tissues.

The numerous mitotic figures in the circulating blood led us to suspect the possibility of multiplication of these cells in the blood. Our experimental work, while not conclusive, leads me to believe, however, that such probably was not the case.

It is not my intention to prove or disprove that "myeloblasts" and "lymphoblasts" are identical cells. I do wish to show, however, that

in this case, great numbers of cells were circulating in the blood, which were morphologically identical with "micromyeloblasts," cells which ordinarily are known to be derived from the bone marrow. We have good evidence that a great many of our "micromyeloblasts" were being generated in the lymphopoietic tissues and were passing out from these tissues into the blood circulation.

Myelocytes were not found on some days, but there were as many as 3 per cent. on other days. No promyelocytes were seen. Nucleated red blood cells were present in small numbers. The appearance of

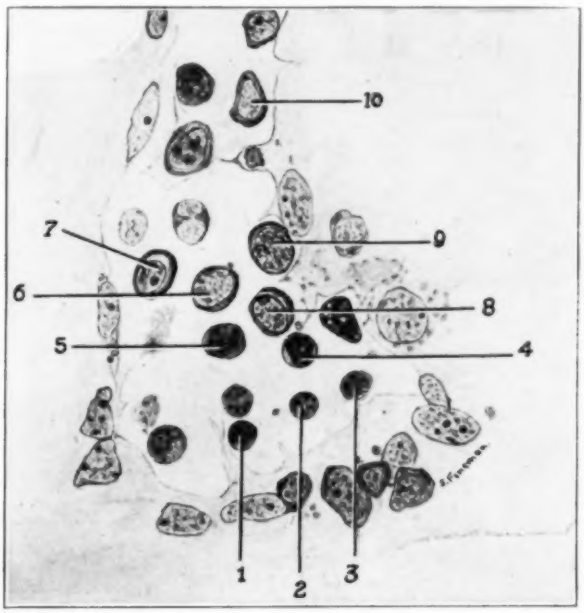

Fig. 17.—Lymph sinus, showing both lymphocytes and stem cells. Objective, 1.5 mm.; Zeiss apochromatic; ocular, No. 8; compensating; Zeiss.

the myelocytes and nucleated red blood cells may be considered as the result of the irritation of the bone marrow due to the severe anemia.

B. Lymph Node.—The lymph node was obtained by biopsy and was immediately fixed in Helly's fluid. The Dominici and methyl green pyronin stains were used. The appearance of the node with a magnification of eight times is represented in Figure 13. With low power, the usual markings of a lymph node are almost obliterated. The structure of the medulla is not as dense as that of the cortex. The follicles of the cortex are not clearly discernible, with the exception

of an occasional one. In examining a hundred sections, only six slides were found showing a single clear follicle containing a germinal center. The remainder of the cortex shows a merging of the follicles with the interfollicular tissue.

The peripheral sinus is filled with cells. The lymph sinuses surrounding the trabeculae are practically all filled with dark staining cells, and the same holds true for the plexus of sinuses throughout the entire node. The medullary cords do not stand out prominently but fuse more or less with the rest of the tissue. The blood vessels contain red blood cells, which are rather indistinct with the low power

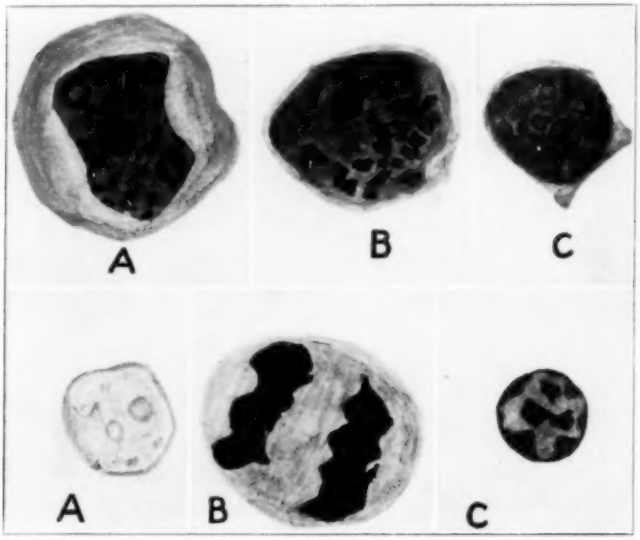

Fig. 18 (Upper).—Objective, 1.5 mm.; ocular, No. 8; magnification, ×8. A. Large lymphocyte with seven nucleoli, in section. B. Medium sized lymphocyte, in section. C. Small lymphocyte, in section.

Fig. 19 (Lower).—Objective, 1.9 mm.; ocular, No. 10; ×8 actual appearance. A. Stem cell, very small, in section. B. Cell in mitosis in the lymph node. C. Small lymphocyte in section.

lens, and white blood cells which show up very distinctly. The capsule is very much thickened and infiltrated. In places it appears to be necrotic. The fatty tissue outside of the capsule is also infiltrated with many dark staining cells. With this low power the Dominici and methyl green pyronin sections show a great many cells which stain paler than the rest.

With the Zeiss apochromatic 1.5 mm. oil immersion lens and the No. 8 Zeiss compensating ocular, it is seen that besides the usual

normal cellular constituents, the entire lymph node is permeated by atypical cells, quite variable in size. Some are larger than the largest lymphocytes to be seen in the node. Others are very small, about the size of a small lymphocyte. The cytoplasm of most of the cells forms a thin ring around the nucleus (Fig. 12c). In a few cells, especially those of the germ center, the cytoplasm projects out in the form of pseudopodia (Fig. 14 Cells 3, 8, 12 and 15). These cells are free and in all probability migratory in nature. The cytoplasm stains basic and is darker than the cytoplasm of the lymphocytes, and has a homogeneous appearance (Figs. 12d and 12c). In some cells the area immediately around the nucleus stains considerably lighter than the peripheral portion. No granules are demonstrable in the cytoplasm of the cells in the sections.

The nuclei, here as well as in the blood cells, form the diagnostic feature of the cell. They are usually eccentrically placed. Some are round, the majority are ovoid, but many are very irregular in shape, especially in the cortical regions, where proliferation seems to be very profuse and the cells are crowded. The nuclear membrane is very thin and hardly to be made out in some cells. The nucleus, as a whole, stains much lighter than the cytoplasm, and can very readily be differentiated from the majority of the nuclei of the lymphocytes which stain considerably darker. Practically all of these atypical cells contain one or more nucleoli. The chromatin arrangement is entirely different from that of the lymphocytes. Whereas the chromatin of the lymphocytes, both large and small, is arranged in blocks, taking a dark stain and usually arranged at the periphery of the nucleus, the chromatin of these atypical cells forms a fine network of tiny particles, which stain very lightly and seem to be linked by fine threads running in every direction through the nucleus. In some nuclei one may observe from one to four very small blocks of chromatin, which stain very lightly and are irregularly placed (Fig. 12d).

The morphology of these cells, therefore, corresponds exactly with the morphology of myeloblasts and micromyeloblasts as decribed by Naegeli, or to the lymphoidocytes of Pappenheim.

Throughout the entire lymph node numerous cells in all stages of mitosis are seen (Fig. 14, Cell 1). The blood vessels show these "micromyeloblasts" in large numbers. They are easily distinguishable from the ordinary lymphocytes. Figure 15 shows a small blood vessel containing a lymphocyte, a "micromyeloblast," and red cells. Occasional mitotic figures can be seen in the lumina of the blood vessels. Figure 16 shows such a figure in a blood vessel.

The lymph sinuses likewise are filled with enormous numbers of these "micromyeloblasts." Figure 17 shows several such cells in a lymph sinus in the cortex of the node. They are here also readily

distinguishable from the large and small lymphocytes. In this figure, cells 6, 7, 8, 9 and 10 are "micromyeloblasts." They are identical with those in the germ center. Cells 1, 2, 3, 4 and 5 are lymphocytes.

The cells of the reticulum proper can easily be differentiated from the lymphocytes and the "micromyeloblasts." The cytoplasm of the reticulum cells is large in amount and stains very lightly. Cytoplasmic processes extend in all directions so that the cell assumes a stellate appearance. The cell membrane is exceedingly fine. In the majority of reticulum cells only part of the cytoplasm is visible, the remainder fading out into the adjacent tissue or being concealed by overlying cells. The nucleus is surrounded by a sharply defined membrane, which in many cells is invaginated and may form long grooves over the surface of the nucleus (Fig. 14, Cells 31, 32 and 34). The nucleus is exceedingly poor in chromatin and appears to be very vesicular. A nucleolus may or may not be present. Occasional small blocks of chromatin may be present. In some cells the chromatin surrounds the nucleolus, in others it is scattered about.

The capsule is thickened and is infiltrated with lymphocytes "myeloblasts" and "micromyeloblasts." Figure 16 shows a small blood vessel of the capsule containing a cell in mitosis. In this figure cell 1 is an endothelial cell; cell 2, a connective tissue cell, and the remaining cells are "myeloblasts." A study of the various cells in the capsule shows transition forms between our "myeloblastic" cells and lymphocytes as well as connective tissue cells. These transition forms are of both large and small cells.

In some places all the cells are flattened and elongated, while in other places actual necrosis is present.

Mitotic figures are also present in the capsule. The "myeloblasts" and "micromyeloblasts" are present in far greater numbers than the lymphocytes. There are also many transition forms between our atypical cells and the lymphocytes, which are recognizable by the fact that in these cells, having all the cytoplasmic and nucleolar characteristics of an atypical cell, some of the chromatin is arranged in the form of dark staining blocks which vary in number in the different cells. The majority of these chromatin blocks are usually to be found at the periphery of the nucleus or abutting the nuclear membrane. Similar transition forms were found in the germ centers of the follicles and will be described in detail under that heading. In the capsule a whole series of cells can be found between our atypical cells and lymphocytes.

We also have evidence indicating relationship between the connective tissue cells of the capsule and our atypical cells. There are typical elongated connective tissue cells, with the clear, pale, almost homogeneous cytoplasmic processes, and vesicular, pale nuclei. The next cell in the series shows a shortening of these processes. Then,

again, a cell may be completely rounded out or oval in shape. These cells take on a more basic stain, which is usually a sign of cell activity, and the nucleus shows more and more the characteristics of our atypical cells.

In the medulla an occasional cord can clearly be made out. The majority of cells in these cords are lymphocytes. However, scattered everywhere among them are our atypical cells. Here, too, mitotic figures are numerous. The rest of the medulla contains a majority of our atypical cells. These are also present in large numbers in the blood vessels and sinuses.

The cortex shows only a very few follicles with germinal centers. In a hundred sections only six were found. Follicles without germinal

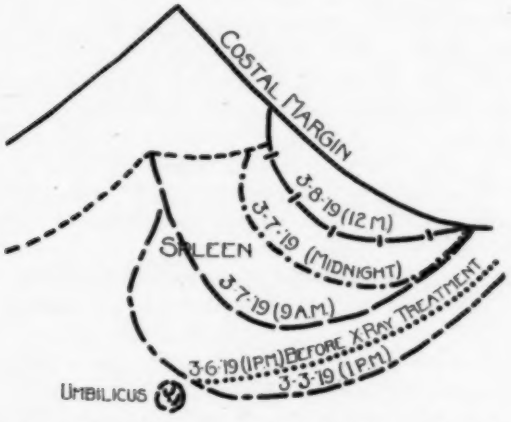

Fig. 20.—Composite tracing showing diminution in size of spleen from March 3 to 8. Roentgen-ray treatment over spleen was given March 6.

centers are more numerous. No signs of follicular atrophy are present. All evidence points toward increased activity. Mitotic figures are numerous. Our atypical cells are present everywhere. Between the follicles they constitute the majority of cells, but they are very numerous throughout the follicle, and are present in large numbers in the very centers of those follicles which do not show germ centers and in the germ centers of the six follicles studied.

Transition forms between our atypical cells and lymphocytes, as well as between lymphocytes and cells of the reticulum, are present throughout the parenchyma of the node.

The germ center of a follicle, as represented in Figure 14, is typical of all other germ centers found.

The "micromyeloblasts" are of about the same size as a small or medium sized lymphocyte (Cell 4). All graduations in size up to the size of a very large lymphocyte are present (Cells 5, 6, 7, 8, 9 and 10). This variation in size is evident throughout the node. With methyl green pyronin the cytoplasm stains an intense red. The red color is more pronounced in these cells than in the cytoplasm of the lymphocytes. In these India ink drawings the red staining cytoplasm is represented by various shades of gray, arranged proportionately to the intensity of the staining reaction. Compare cytoplasm of Cell 11, a lymphocyte, with that of Cell 7, a medium sized "myeloblast." Light staining areas in the cytoplasm (Cell 12), or around the nuclear membrane (Cells 5 and 9) are present. The shape of the cell varies considerably. It may be round (Cell 4) or oval (Cells 2 and 7) or considerably elongated (Cells 13 and 8). Some of the cells are more or less angular, like Cells 9 and 14. Pseudopodia-like cytoplasmic processes are to be seen on some cells, probably indicating their migratory nature (Cells 3, 8, 12 and 15). The cytoplasm appears to be homogeneous and no granules are distinguishable with either the methyl green pyronin or Dominici stains. The cytoplasmic rim varies in size. In the majority of cells it is rather narrow but well defined (Cells 3, 6 and 7). In some cells it is considerably larger (Cells 8, 9, 10 and 12).

The nucleus may be placed eccentrically or centrally. In the majority of cells it is eccentric. The nucleus is large and occupies the greater portion of the cell. It varies greatly in shape. It may be round, oval, or angular (Cells 6, 7 and 9). Bottleneck-like constrictions may occur (Cell 16).

The nuclear membrane is well defined but thin. It may invaginate the nucleus and form folds which may be mistaken in cross section for nucleoli. Cell 10 shows three such invaginations, which could easily be mistaken for nucleoli, since the nucleoli and the cytoplasm both stain red. Careful focusing, however, shows these to be continuous with the cytoplasm.

One or more nucleoli are usually present. These take the pyronin dye and stain red. They may be located anywhere in the nucleus and vary considerably in size. Compare nucleoli in Cells 2 and 9. Small masses of chromatin may surround the nucleoli (Cell 12).

The arrangement and quantity of the chromatin is the chief diagnostic characteristic of the cell. The chromatin and parachromatin are approximately equal in amount. The chromatin, taking a dark greenish violet stain with methyl green pyronin, is in the form of extremely fine dustlike particles, scattered rather uniformly throughout the entire nucleus (Cells 2, 6, 9 and 12). In some cells coarse chromatin masses are entirely absent (Cell 6), while in others, one or more may be present (Cells 7, 10 and 13).

The ordinary lymphocytes are easily distinguishable from our atypical cells. They vary greatly in size (Cells 17 and 18). Their cytoplasm also takes the red stain, but not so intense a red as the cytoplasm of the atypical cells. In the majority of lymphocytes, the cytoplasm forms only a very narrow rim about the nucleus, visible only where the nuclear membrane is invaginated (Cell 19), or only on one side of the cell (Cell 11), or not at all (Cell 18).

The nuclei of these lymphocytes are also characteristic. They stain considerably darker than the nuclei of the atypical cells (Cell 18). Numerous coarse chromatin strands run in all directions. Chromatin blocks, triangular, square, oblong and irregular in shape, are present. These, in many cells, have a tendency to arrange themselves around the nuclear membrane (Cell 20). Nucleoli may be, but usually are not present.

In this germ center (Fig. 14), as well as throughout the parenchyma, many transition forms between lymphocytes and our atypical cells may be seen. Beginning with a cell like Cell 6, which represents a fairly small "myeloblast," we may find a cell like Cell 22. In this cell the nucleolus is surrounded by chromatin, and small masses of chromatin line the nuclear membrane. Two other chromatin blocks are to be seen below the nucleolus. The cytoplasm does not show any changes.

The next in the series would be one like Cell 5. In this cell the chromatin blocks are more numerous and larger. A nucleolus is present. The nucleus is indented in several places. The cytoplasm stains a slightly lighter red.

The next stage is represented by Cell 23. The cytoplasm is definitely less red than in Cell 5. The nucleus still retains the basic character of a "myeloblast." It is lightly stained and fine dustlike particles of chromatin are in evidence everywhere. Here, however, there are eight triangular shaped, dark staining, large chromatin blocks arranged in "radkern" fashion about the nuclear membrane. In addition four more or less large irregular chromatin blocks, and several smaller blocks occupy the central portion of the nucleus. At first sight such a cell has all the earmarks of a lymphocyte. A detailed and careful study and a comparison with typical lymphocytes and "myeloblasts" shows that it is neither one nor the other but a cell which must be placed halfway between the two.

The next cell in the series is Cell 24. In this cell the cytoplasmic rim is considerably narrowed, and is practically invisible in part. The nuclear membrane is thick and is lined all the way around with chromatin strands and blocks. Numerous coarse chromatin blocks and strands are to be seen in the finer chromatin groundwork described

for the "myeloblast." This cell is past the half way mark in the transition series.

Cell 25 is practically a normal lymphocyte. In comparing it with Cell 18, which I consider to be a typical lymphocyte, the only diagnostic differential point is the character of the nucleus. The nucleus of Cell 25 is practically a lymphocyte nucleus. However, it lacks the coarse irregular chromatin strands so frequently found in lymphocytes, and it still shows a rather fine distribution of small chromatin particles all through the nucleus.

Other cells which I consider as transition forms are Cells 26, 27 and 28. And so thoroughout the parenchyma of the lymph node complete series of transition forms are present. Whether the lymphocyte is the mother cell of our atypical cell or vice versa, I do not know. Our evidence is such as to show a relation between the two types of cells.

Another type of cell present (Fig. 14, Cells 31, 32, 33 and 34) is the reticulum cell. This cell varies considerably in size and can very easily be differentiated from the various types of lymphocytes, atypical cells and transition forms. The cytoplasm of this cell takes an extremely light pinkish stain. In most of the cells, as in Cells 31 and 32, no definite cytoplasmic rim can be made out. Cell 34 shows the cytoplasm and the cytoplasmic processes very well. The nuclei of these reticular cells are very vesicular. The nuclear membrane is sharply outlined. The nucleus may be almost triangular in shape, as in Cell 31, or oval shaped, as in Cell 32, or elongated, as in Cell 33. The chromatin content is extremely meager, as in Cells 31, 32 and 33. It usually consists of a few small blocks and a few strands. A rather large nucleolus, staining red, and usually surrounded by some chromatin may be present (Cells 31 and 32). Here, too, there is evidence showing a relationship between our atypical cells and the reticulum cells, as well as a relation between the reticulum cells and the lymphocytes.

A rather incomplete series may be represented by Cells 23, 28, 35 and 36, respectively. The nucleus of a small reticulum cell is shown in Cell 35. Cell 36 shows a beginning formation of chromatin blocks and a darkening of the karyoplasm. Cell 28 shows a small amount of well defined cytoplasm, the nucleolus is prominent and chromatin arrangement and karyoplasm staining are suggestive of a cell between a "myeloblast" and lymphocyte, as well as between a lymphocyte and a reticulum cell. Cell 23 might very well fit in as the next in the series. It has already been described as a transition cell between a lymphocyte and a myeloblast, so that by including it also in our reticulum lymphocyte series I believe to have demonstrated a relation between the reticulum cells, lymphocytes and atypical cells. This relation of reticulum cells to the other two is not as definite as the relation between lymphocytes and the atypical cells. Not enough transition

stages are shown in this one germ center. A study of other parts of the parenchyma reveals much more conclusive evidence.

In comparing our atypical cells with the various cells found in supposedly normal lymph nodes, human and animal, I did not find any cells at all comparable to our "myeloblasts" and "micromyeloblasts." Even germ centers cells, the so-called "lymphoblasts" were not comparable to our atypical cells. In these "lymphoblasts" the cytoplasm takes on a lighter stain, and the chromatin occurs as fairly coarse dark staining blocks. The fine dustlike particles of chromatin scattered fairly uniformly throughout the entire nucleus are lacking.

DISCUSSION

It should be pointed out, that in comparing cells in blood smears with cells in sections we must keep in mind certain morphologic differences which are always present, due to the difference in technic. In making a blood smear, the drop of blood is quickly spread out over the slide and dried. The capillary traction flattens out the cells so that they appear much larger than they actually are. In sections, however, the various cells are exposed to the action of fixing fluids and consequently undergo a certain amount of shrinkage, even with the best of fixing fluids such as Helly's solution. Furthermore, an identical Wright's stain technic cannot be used satisfactorily in sections and blood, so that in comparing blood and tissue cells one must bear this also in mind.

In comparing a normal lymphocyte in the blood with a normal lymphocyte in sections we notice a definite morphological difference. The chromatin of the blood lymphocyte is arranged in a more or less definite network, while in the lymphocytes of sections the chromatin is arranged in coarse blocks and irregular strands. The lymphocytes in the blood vessels of sections also show these coarse blocks and irregular strands. The same holds true for myeloblasts in the blood and in sections. Whereas, myeloblasts in the blood show a beautiful sievelike nuclear chromatin network, in the tissues there is more of a tendency to formation of fine particles with occasional chromatin block formation. This same change is also evident in the myeloblasts in section blood vessels.

The "micromyeloblasts" and "myeloblast" are very frequently mistaken for lymphocytes, because they overstain very easily, thus losing their typical appearance.

The presence of the stem cell (microlymphoidocytes and lymphoidocytes of Pappenheim or micromyeloblasts and myeloblasts of Naegeli) in large numbers in the blood of leukemics is usually associated with an acute and rapidly fatal course of the disease.

A blood picture alone will often lead to a wrong diagnosis. In some cases, for a correct diagnosis, histologic studies must supplement

the blood studies. Krjukoff diagnosed myeloid leukemia from the blood, yet the bone marrow showed only slight activity and he was forced to conclude that his myeloid cells were coming from the "myeloid parts" of lymph nodes and spleen.

Similarly, Citron diagnosed "micromyeloblastic" leukemia, yet he found the bone marrow normal and lymph follicles hyperplastic and proliferating these "myeloid" cells.

The dualists, however, deny the possibility of "myeloid" cells originating from lymphatic tissue. They argue that in lymphatic leukemia the follicles of the lymph nodes atrophy or are, at least, quiescent. They deny absolutely the possibility of "myeloid" cells ever occuring in follicles and especially in the germ centers of follicles.

Citron's case, however, showed the "myeloblasts" of the dualists in the follicles of the lymph nodes and spleen.

Naegeli, referring to Citron's case, belittles the findings because "the patient died as a result of overdosage of benzol." Only one dose of 6 gm. was given by rectum. Boni [87] gave 5 gm. daily for three weeks. Josefson [88] gave 96 gm. in six weeks. Krokiewicz [89] gave in one case a total of 206 gm. No ill results were observed in these cases.

Naegeli also belittles the findings in cases which had excessive roentgen ray therapy.

The patient at the time the axillary lymph node, on which this study is based, was removed had not had any benzol, nor had there been any direct roentgen-ray irradiation of the axillary lymph nodes.

We believe our case to be even more convincing than Citron's for two reasons: The lymph node was obtained in vivo, so that postmortem changes can be ruled out. Whereas, Citron speaks of "myeloblasts" and "micromyeloblasts" in the follicles he does not say that he found them in the germ centers. The germ centers in our cases contained many of these cells.

This case is presented in the belief that it offers evidence in favor of the unitarian theory of Pappenheim and Ferrata. The cell which has been described as a "myeloblast" and which the dualists have assumed to be a specific myeloid cell was found to originate in the germ centers and follicles, as well as in the medullary portion of the node. This case and the case reported by Citron prove, therefore, that the cell in question may be related to lymphocytes as well as to cells of the myeloid series.

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87. Boni: Sur une cas de leukémie chronique myeloide traitée par le benzol, Bull. delle clin. (Aug.) 1913; abstr. in Folia haematol. **16**:167, 1914 (Aubertin).

88. Josefson, A.: Benzolbehandlung vid Leukämi, Hygiea, 1914 (abstr. Folia haematol. **16**:167, 1914).

89. Krokiewicz, A.: Die Benzol Behandlung der Leukämie, Przegl. lekarski **52**:582, 1913 (abstr. in Folia haematol. **16**: 169, 1914)

SUMMARY

Morphologic Part 2

1. The blood, at all times, showed numerous stem cells (lymphoidocyted of Pappenheim), (myeloblasts of Naegeli) of all sizes. Our cells, which we shall refer to as atypical cells, had a basophilic cytoplasm and a nucleus in which the chromatin formed a very fine evenly distributed sievelike network. Morphologically our atypical cells were indistinguishable from typical myeloblasts.

2. Very careful staining was essential in bringing out the finer details of these atypical cells.

3. The oxydase reaction was negative in these cells in the blood smears.

4. The diagnosis from the blood alone would be "micromyeloblastic" leukemia.

5. The presence of numerous mitotic figures in the blood stream suggested the possibility of cell proliferation in the blood stream. We could not demonstrate such to be the case.

6. Lymphocytes, normal in appearance were always present in the blood. The contrast between the lymphocytes and the atypical cells was very marked. Numerous transition forms between the lymphocytes and the atypical cells were present in the blood.

7. Some myelocytes and nucleated reds were present. The severe anemia might easily account for these.

8. The biopsy of a lymph node showed these atypical cells proliferating in great numbers in the capsule, interfollicular tissue, lymph cords, lymph follicles and in the germ centers of the lymph follicles.

9. Transition forms between the connective tissue cells of the capsule and these atypical cells as well as between lymphocytes and these atypical cells were present in the capsule.

10. In the interfollicular tissue as well as in the follicles and even in the germinal centers transition forms between these atypical cells and reticulum and lymphocytes were also present.

11. The lymph follicles and lymph cords showed no signs of atrophy, but had all the earmarks of marked activity. Mitotic figures were numerous. The only signs of atrophy or necrosis were found in the capsule.

12. These atypical cells formed the majority of the cells of the parenchyma.

13. These atypical cells constituted by far the majority of the cells in the lymph sinuses and were very numerous in the blood vessels of the node.

14. From the evidence at hand, the conclusion is justified that in all probability the majority of the "myeloblasts" and "micromyeloblasts" of the blood were coming from the lymphoid organs, not only from the portions which, according to the dualists, may give rise to myeloid cells, but from the sanctum sanctorum of the lymphoid tissues, namely, the follicles and germ centers.

I wish to express my sincerest thanks to Professors L. G. Rowntree and S. Marx White for their kind guidance in the preparation of the clinical report, and to Professor Hal Downey who was the first to recognize the significance of the case and under whose direction the morphologic study was carried out.

INTRACUTANEOUS REACTIONS IN LOBAR PNEUMONIA *

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In 1915, Clough [1] reported intracutaneous reactions in lobar pneumonia patients. He prepared his antigen as follows: Cultures used were made from the lungs in cases of fatal pneumonia, with no statement as to type. From twenty-four to thirty-six hour old cultures in 5 per cent. glucose broth plus calcium carbonate were decanted off the carbonate, centrifuged, washed with salt, recentrifuged, the sediment taken up in a few drops of distilled water, dried, weighed, ground for three hours with sterile sand, extracted with 10 c. c. saline for each gram of dried material, incubated for eighteen hours; centrifuged at high speed for several hours until no more sediment came down; used in this form or precipitated with absolute alcohol. One gram of the dried culture residue yielded about 0.15 gm. dried alcoholic precipitate.

He used two methods of inoculation: first, allowing a drop of 1 per cent. solution of his antigen to dry on a scarification as for a von Pirquet tuberculin test; second, injecting a 0.25 per cent. solution intracutaneously, causing a painful inflammatory reaction subsiding after twenty-four hours. There was no appreciable increase in severity or time of the reaction in the pneumonias over the controls. The more dilute solutions gave discrete papules from 0.5 to 2 cm. in diameter with an ill-defined area of hyperemia. The actual measurements of the papules averaged a little larger in the pneumonias, but this was only slight and inconstant. He found no difference in reactivity early, at crisis, or later in convalescence. As to Clough's work, then, it may be said that he used a rather elaborately prepared antigen with practically negative results.

Weil [2] criticizes Clough's antigen for being too strong so that it produced reactions independent of any immunologic response. He used forty-eight hour old cultures on Loeffler's serum medium suspended in distilled water, from 2 to 3 c. c. to a tube, shaken, incubated two hours, and then heated to 60 C. for one hour. In a few early experi-

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* This article is one of a series of studies carried out under the supervision of the Influenza Commission of the Metropolitan Life Insurance Company. The Influenza Commission is investigating the etiology and prevention of the acute respiratory diseases, and the work is being carried on in Boston, New York, Chicago and Washington. The members of the Commission are Dr. M. J. Rosenau, Chairman, Dr. G. W. McCoy, Dr. L. K. Frankel, Dr. A. S. Knight, Dr. E. O. Jordan, Dr. W. H. Frost and Dr. W. H. Park, Secretary.

1. Clough, P. W.: Johns Hopkins Hosp. Bull. **24**:295, 1913.
2. Weil, R.: J. Exper. M. **23**:11, 1916.

ments a Type III organism was used "with success," otherwise Type I was used exclusively. For the test, a sufficient amount of antigen was injected to produce a small wheal, that amount being between 0.1 and 0.2 c. c. All showed an immediate superficial ill-defined blush which was considered merely traumatic. In the negatives this faded within a few hours and nothing more developed. In the positives, within twenty hours a fairly well circumscribed area of erythema had developed with slight infiltration and elevation of the skin surrounding the point of puncture. This may be a true papule, persisting for forty-eight hours or even longer. Weil obtained no reaction during the course of the disease, but "after the subsidence . . . a considerable percentage of cases do present reactions." These exceptionally appeared twenty-four hours after crises, but more commonly later even after two, three or more weeks. The controls "may or may not present a reaction dependent presumably on their previous sensitization by the pneumococcus or an allied organism." A few cases of pneumonia gave no reaction at any time. In summary, Weil obtained positive reaction in a "considerable percentage of cases" after crisis, and in some controls. The reaction which he considered positive reached its maximum within twenty hours, though it might persist for two days or more. He used a relatively simple incubated suspension of pneumococci in distilled water.

Steinfield and Kolmer[3] prepared an antigen in much the same way, except that they suspended in saline instead of distilled water and omitted the incubation. Separate preparations of Types I, II and III were made. The final dilution was such that 1 c. c. contained 2 billion cocci, that is 200 million were injected for a test. They found that at the end of twenty-four hours all tests showed a zone of hyperemia. By forty-eight hours a definite papule had appeared in the positives, with an erythema greater than 1 cm. in diameter and accompanied by slight edema. This reaction persisted for four to five days, and gradually cleared. There was no instance of a pustule formation. In the negatives the erythema had largely cleared by forty-eight hours. Of nineteen cases of clinical lobar pneumonia, six gave positive reactions with one or more antigens. But in none did the type or types found in the sputum exactly correspond with those shown by the skin reaction. For instance, one case showed Type I in the sputum and reacted to Types I and III; another case showed Types I and II in the sputum and reacted to Types II and III, etc. The earliest reaction appeared on the ninth day of the disease, or three days after crisis, and the latest on the thirty-ninth day after onset. "A large number of tests with healthy persons and patients suffering from chronic ailments not involving the chest" were negative. The

3. Steinfield, E., and Kolmer, J. A.: J. Infect. Dis. **20**:344, 1917.

authors conclude that there is no constant relation between the reaction in the skin and the type of organism found in the sputum, and think it probable that the allergic reactions to pneumococcus protein are of a more general character than the agglutination reactions.

In 1918 Weiss and Kolmer [4] report an intracutaneous test with a preparation of "pneumotoxin" as opposed to the "pneumoprotein" of the former tests. Perhaps the most important difference in their antigen over those used previously is that at no time is the product heated to a temperature which would endanger the thermolabile substances. They centrifuged eighteen hour broth cultures of Type I pneumococcus, washed once with saline, took up in 5 c. c. saline and dissolved the cocci in 1 c. c. of a 2 per cent solution of sodium choleate. The total volume was made up to 30 or 40 c. c., centrifuged to remove undissolved pneumococci and 0.2 per cent. tricresol added. The "control fluid" was treated as above, except for the inoculation with pneumococci. The minimal lethal dose for a 250 or 300 gm. guinea-pig was found, and the antigen diluted so that 0.1 c. c. contains one twentieth the minimum lethal dose (M. L. D.). This amount was injected intracutaneously for the test. The preparation deteriorated rapidly and was made fresh every day. The authors found the reaction in "all respects similar to that described for the Schick test with diphtheria toxin." Cases just prior to the crisis showed a strongly positive reaction marked by vesiculation. Others showed a definitely circumscribed area of edema and erythema gradually fading, leaving a scaling zone of brownish pigmentation. The "control fluid" and heated "pneumotoxin" remained negative. Pseudoreactions involving the entire arm with diffuse erythema and a definite area of edema never persisted longer than forty-eight hours. Of thirty-eight cases of "acute lobar pneumonia" all reacted positively; of sixteen cases of "lobar pneumonia convalescents" five reacted positively; of five "doubtful" cases ("alcoholism and tuberculosis with possible superimposed pneumonia"), one gave a positive reaction; and of twenty-three controls all were negative.

In summary, they state that the tests with "pneumotoxin" were elicited as early as the fifth day (the earliest under observation) and as late as the thirteenth day of the disease. In general, the test was positive throughout the toxemia.

Further in the paper the authors took up the question of the type specificity of this reaction. The sputum from ten cases which reacted positively to their type I "penumotoxin" was examined for type organism. Six of these showed Type IV and four showed Type I. They consider that "sensitization to the toxin presumably takes place with its liberation (by action of normal enzymes on pneumococci normally

4. Weiss, C., and Kolmer, J. A.: J. Immunol. **3**:395, 1918.

localized in the lung alveoli) at the time of the prolonged chilling due to exposure." They feel that the method is not as yet of value in serologic type diagnosis.

In these two papers Kolmer shows that his heated saline suspension of pneumococci gives positive reactions after crisis which are not specific for type, and that his unheated bile salt solution of pneumococci gives positive reactions before as well as after crisis which are also not specific for type. It is rather a surprise after having compared this latter reaction to the Schick test in diphtheria, to find that the presence rather than the absence of a reaction is considered specific. The authors' theory of early sensitization against their "pneumotoxin" is certainly open to question when we consider the absence of any sensitization necessary in the case of the positive Schick reaction, and also the lack of specificity in the toxic radicle as shown by Vaughan's work.[5]

EXPERIMENTAL WORK

It was hoped that by the study of a considerable series of pneumonia cases and normal and diseased controls, using antigens made from the various types of pneumococci (homologous and heterologous) prepared in various ways, additional information might be obtained concerning the rôle played by allergy in pneumonia with especial reference to crisis. Furthermore, it was hoped that by varying the method of preparation and dose of antigens prepared from the various types of pneumococci, it might be possible to obtain antigens sufficiently delicate to indicate the type of infection present. If this reaction should prove to be positive in the early stages of the disease, it might furnish an earlier, quicker and simpler means of type determination than can be obtained by the present method of mouse inoculation, thus making it possible to institute specific serum therapy in suitable cases with less loss of time than is at present possible.

Cultures and Their Sources.—The cultures [6] used in the preparation of antigens were:

5. Vaughan, V. C., and Wheeler, S. M.: J. Infect. Dis. **4**:476, 1907.

6. The cultures used were obtained as follows: I A from Dr. F. T. Lord. I B, II A, II B, III A and III B from Dr. G. B. White, State Biological Laboratory, Forest Hills. IV B and IV C from Miss E. A. Beckler, Bacteriological Laboratory, State House, Boston, isolated Dec. 13, 1920. The remaining cultures were isolated in the Pneumonia Laboratory of the Department of Preventive Medicine and Hygiene. The following were obtained from blood cultures taken on patients on the Special Pneumonia Service at the Boston City Hospital on the dates as indicated: I C, Jan. 15, 1921; I D, January 24; I F, Feburary 24; I G, February 18; I H, Feburary 28; I J, March 15; III C, February 15; III D, February 27, and IV E, January 24. The following cultures were isolated from the sputum of similar patients: I E, February 8, and I I, March 22. The following cultures were isolated from the sputum of patients outside Boston as indicated: IV A, Foxboro State Hospital, and IV D, Framingham.

Type I: 10 strains, designated I A, I B, etc.

Type II: 2 strains, designated II A and II B.

Type III: 4 strains, designated III A, III B, etc.

Type IV: 5 strains, designated IV A, IV B, etc.

Methods of Preparing Antigens.—The cultures used were from eighteen to twenty-four hour old growths in 100 c. c. of a 1 per cent. glucose beef infusion broth, neutral to phenolthalein, which was found to correspond to a hydrogen ion concentration of from 8.0 to 8.2. On this medium there was homogeneous clouding of the broth with an abundant sediment in the bottom of the flask. The morphology of the organisms used was typically that of pneumococcus, gram-positive, bile soluble, and the type was repeatedly verified by agglutination with type serum from the New York State Board of Health and the Rockefeller Institute. All growths were examined microscopically for contamination, and serologically to confirm the previous type determinations.

For all the antigens, the first steps were identical. The growth was centrifuged, and the sediment was washed twice with sterile salt solution, centrifuging after each washing. Throughout the work the centrifuge was run at about 3,000 revolutions per minute. The time interval for centrifuging and shaking electrically was one-half hour.

The finished antigen was sealed in ampules containing sterile glass beads so that if desired the suspension could be shaken thoroughly before use to insure uniformity of material. Whenever the antigens were heated to 56 C. special care was taken that the entire ampule was completely submerged in the water bath. Before using the antigens were plated on whole rabbits' blood agar to test sterility, and in the simpler preparations bacterial counts were made according to Wright's method [7] as commonly used in standardizing bacterial vaccines. The ampules were kept on ice until used. No antigen was used more than a week after being put on ice. Both the opalescent supernatant fluid and also the entire opaque suspension of organisms were used. Before using the antigens were diluted with sterile saline solution and doses varying from 10 to 1,000 million bacteria or their equivalent were injected in 0.1 c. c. volume.

With the earlier antigens the strains (except Type IV) were kept separate. Thus a patient with a known Type I pneumonia might be inoculated with four strains of Type I, one strain each of Types II and III, and a polyvalent Type IV, the whole constituting one test. No especial merit was found in this method, the few homologous strains used giving no better results than the heterologous strains, and since it subjected the patients to multiple inoculations, the strains of each

7. Wright, A. E.: Lancet **2**:1556, 1900; **2**:11, 1902.

type were pooled. The Type IV antigen was later omitted since in specific reactions the two nonspecific types furnished ample controls.

Antigen 1.—Cultures I A and I B, II A and II B, III A and IV A, IV B and IV C were used. The sediment after the second washing was taken up in from 20 to 30 c. c. of saline solution and heated to 56 C. for one hour. The ampules were then vigorously shaken, and put on ice.

Antigen 2.—Prepared as Antigen 1, except that it was incubated one week before being used. At the end of that time the sediment formed on standing showed on smear much amorphous gram-negative material including faint staining cocci with individual gram-positive cocci and rare diplococci.

Antigens I C and I D.—These were prepared as Antigens 1 and 2 from cultures I C and I D. They were used autogenously and on a few other patients.

Antigen 3.—Prepared as Antigen 1 with the following cultures: I A and I B; II A and II B; III A and III B; and IV A and IV C.

Antigen 4.—Same as Antigen 3, except that it was incubated one week.

Antigen 5.—Same as Antigen 4, except that it was incubated two weeks before using.

Antigen 6.—After the second washing with saline solution, the sediment was taken up with distilled water instead of saline solution. Cultures used: I A, I B and I C; II A; III B; IV A, IV C, IV D and IV E.

Antigen 7.—Same as Antigen 6, except that it was incubated one week.

Antigen 8.—After the second washing with saline solution, the sediment was taken up in 10 c. c. of a 10 per cent. bile solution,[8] and incubated for one hour. Attempts were made to obtain suitable animal membrane for separation of the bile salts from the dissolved pneumococcus substances by dialysis, but it was found more feasible to obtain the separation by precipitation of the protein with four volumes of absolute alcohol. This was thoroughly shaken, centrifuged and the sediment again mixed with absolute alcohol. After recentrifuging, the sediment was dried overnight in partial vacuum over sulphuric acid. The residue was weighed, ground with sufficient sodium chlorid to make the final solution physiologic and taken up by adding distilled water drop by drop while grinding until 0.1 c. c. contained 1/150 mg dried sediment.[9] (Later injections up to 1/10 mg. were used.)

8. Bacto-oxgall was used.
9. Gay, F. P. and Minaker, A. J.: J. A. M. A. **70**:215 (Jan. 26) 1918.

This was heated to 56 C. for one hour. For this antigen all the strains of each type were pooled. The cultures used were: I A, I B, I C, I D and I E; II A, and II B; III A, III B and III C.

Antigen 9.—After the second washing with saline solution, the sediment was taken up in a small amount of saline solution and precipitated with four volumes of absolute alcohol. This was centrifuged and taken up a second time in absolute alcohol. After again centrifuging the sediment was extracted by thoroughly shaking with ether. The sediment was dried for one hour in the incubator, weighed, and ground with sufficient salt to make the final solution physiological, and taken up in distilled water, added slowly while grinding. The dilutions were such that the antigen contained 20/150 mg. per 0.1 c. c. This was at first diluted twenty times before using but was eventually used full strength. The antigen was heated to 56 C. for one hour. In this preparation the strains of each type were pooled. The cultures used were: I A, I B, I C, I D, I F, I G, and I H; II A and II B; III A, III B, III C, and III D.

Antigen 10.—The most important difference between this and the foregoing antigens is that it was at no time raised above 37.5 C. The strains of each type used were pooled and were as follows: I B, I C, I D, I G, I H, I I and I J; II B; III C and III D. After the second washing with salt solution the sediment was divided into known amounts and kept on ice. The day of the tests, sufficient of sterile solution of 2 per cent. bile plus 0.25 per cent. tricresol was added to make 0.1 c. c. contain the equivalent of one twentieth of the growth of pneumococci on 60 c. c. of broth.[10] An incubated solution of 2 per cent bile plus tricresol was used as control.

In summary, the first seven antigens were simple suspensions of pneumococci in saline solution or distilled water. Antigens 1, 3 and 6 were not autolyzed in the incubator, while antigens 2, 4, 5 and 7 were incubated one week or more. In antigens 8 and 9 the pneumococci were treated with bile and alcohol, and alcohol and ether, respectively. Thus the pneumococcus protein was subjected to considerable violence. Antigen 10 differed from all the others in that it was never raised above 37.5 C., while the others were all held at 56 C. for one hour. In the bile solution whatever endotoxins the pneumococci contain should be liberated.

Tests.—A "test" consisted of multiple inoculations. In the first seven antigens each strain of the different types was made up separately, with the exception of Type IV strains which were pooled and served

10. Cole, R.: J. Exper. M. **16**:644, 1912; **20**:346, 1914. Avery, O. T., Chickering, H. T., Cole, R. and Dochez, A. R.: Acute Lobar Pneumonia, Prevention and Serum Treatment, Monograph No. 7, Rockefeller Institute for M. Res., 1917. Weiss, C.: J. M. Research **34**:103, 1918.

as a control for the reactions which might be specific for type. Thus, with these antigens, a Type I pneumonia might receive from one to four different strains of Type I antigen, besides one Type II, one Type III and the pooled Type IV antigen. As it was very exceptional to obtain a reaction with one strain and not with all of the same type used (this occurred only in Case 7, which on the thirty-eighth day of the disease responded positively to the homologous strain and negatively to the heterologous strains of Type I), this method was abandoned later, since it subjected the patient to the discomfort of multiple inoculations.

Antigens 8, 9 and 10 were made from pooled strains of each of the fixed types. Type IV was no longer used, since in specific type reaction the two nonspecific type antigens acted as ample controls. Thus with these antigens a "test" consisted of three inoculations, one for each of the three fixed types.

With each new antigen various dilutions of each strain or pooled type were injected in an effort to obtain the titre of the antigen for both the specific type reactions and also for those reactions which did not show type specificity. These titres were, unfortunately, found to be very close to each other, and varied within considerable limits with each preparation and individual.

As stated earlier, tests were performed with both the opalescent supernatant fluid and the whole thoroughly mixed opaque antigen. In general, the supernatant fluid gave fewer reactions that were nonspecific for type, but it was also feared that in the same dilutions it might also elicit specific type reactions with less constancy.

The tests were made on the flexor surface of the forearms. A 26 gage needle was used and 0.1 c. c. was injected intracutaneously. When properly done a bleb appeared which persisted for some minutes; there was pitting at the hair follicles, and no bleeding at the point of inoculation.

Readings.—The tests were read, as a routine, after two, eighteen, twenty-four, thirty, forty-eight and seventy-two hours. Additional readings were made on the positive reactions.

Reactions Appearing with Only One Type of Pneumococcus.—The reactions in this group were at their height in from twenty-eight to thirty-two hours. These showed a deep red, indurated, papular center measuring from 2 to 4 cm. in diameter. Around this there was a somewhat lighter areola measuring up to 8 cm. in diameter. In forty-eight hours the papule still persisted, usually duller in color, the areola had entirely faded and in about half the cases was replaced by a zone of pigmentation. The papule in some cases persisted to the sixth day after the test. In one case there was very fine scaling. In some cases this type of reaction showed nothing after eighteen and twenty-

four hours. In others there was the reaction described below which was fading in twenty-four hours. The reaction to but one type of the antigen used was, in general, specifically positive for the type of infection, and will be referred to hereafter as specific type reaction.

Reactions with Two or More Types.—These reactions were at their height in eighteen hours. They showed no distinct differentiation between central papule and surrounding areola, and were usually indefinite in outline, fading gradually into the surrounding normal skin. The erythema was often mottled and of large dimensions up to 10 or 12 cm. in the longest axis which was always parallel to the long axis of the arm. On fading, unless they later showed specific type reaction, there was no pigmentation or scaling. By twenty-eight hours there remained only a small area about 0.5 cm. across of local redness around the point of inoculation. This reaction was always elicited with more than one of the types of the antigen used and generally with all when all types were used in the same strength. In an individual showing this reaction the number of types in which it appeared seemed, in general, to depend on the strength in which the type antigen was used and in no case on its specificity for the type of infection present. As will be discussed later these reactions were considered as a response to some substance possessed in common by all types of pneumococci or to some property of the antigen not even specific for the entire pneumococcus group. This reaction which was elicited in common by all types of pneumococci will be referred to hereafter as the common reaction.

In an effort to increase the number of specific type reactions, the strength of the antigens was varied with the object of reducing the common reactions to a minimum and yet retain sufficient strength to elicit the reaction to a single specific type.

Special reference must be made to the reactions obtained with Antigen 10 in which the thermolabile toxic substances from the pneumococcus were not destroyed. When used in the strength recommended by Kolmer [4] and in weaker dilutions, severe local reactions were elicited, showing papules becoming pustular with wide zones of erythema and induration up to 12 or 14 cm. in their longest dimension. This was at its height in about thirty hours when the erythema faded, leaving no pigmentation or scaling in any case. The pustule persisted for weeks. This reaction was well marked in both controls and pneumonia cases, the most severe being in a normal control. The control injection of bile and tricresol showed only a small local papule, but none of the violent erythematous and edematous reaction.

Results.—During the course of the work, 124 persons were tested, as follows: (1) Lobar pneumonia, 104 cases; forty-seven had a Type I infection (specific antipneumococcus serum being used in twenty of

these and not used in twenty-seven); eight had Type II infections; seven had Type III pneumonia, one had Types II and III, twenty-nine had Type IV, and in twelve the type was not determined (no atypical Type II cases presented themselves); (2) controls, twenty persons, of whom sixteen were patients showing for the most part acute febrile conditions other than lobar pneumonia, and four were apparently normal. On these 124 persons, 223 tests were performed, divided about equally between the ten antigens. The earliest test was performed on the third day of the disease and the latest on the eighty-first day. The number of tests on each individual varied from one to five.

Of the 104 cases of lobar pneumonia tested, eleven (10.5 per cent.) gave specific type reactions, forty-six (42.3 per cent.) gave a common reaction and fifty-two (50 per cent.) gave no such reaction. Of the twenty controls, none gave a specific type reaction, nine gave a common reaction and eleven gave no reaction.

The eleven cases which gave specific type reactions were distributed among the types of infection as follows:

TABLE 1.—Cases Manifesting Specific Type Reactions

Type of Pneumonia	Number of Cases Tested	Number Showing Specific Type Reaction	Per Cent. Specific
I	47	6	12.7
II	9	2	22.2
III	8	1	12.5
IV	29	2	6.8

This reaction was specific for the type of infection in the patient as determined in the blood or sputum, or both, except with Antigen 9. With this antigen, reactions were elicited in three patients, in each case with the Type II preparation; while with Types I and III preparations the reactions were consistently negative. Of these patients one showed a Type II pneumococcus in the sputum, one a Type I and one a Type IV. In the last two cases blood cultures were persistently negative and repeated examinations of the sputum failed to show a Type II organism. In the Type I patient, the test was repeated with the same antigen five days later and was negative. In the cases of Type I and IV pneumonias, the reaction with Type II antigen was obviously nonspecific as to type of pneumococcus. Although this Type II preparation of Antigen 9 gave frequent negative tests in other cases, it is not unlikely that its apparent specific reaction in one case may be accounted for on the law of chance. Thus all three reactions might well be considered as nonspecific for type, and as a response to some form of protein common to all types of pneumococci, though in that case the Type I and III preparations should also have shown positive reactions, or to some other factor in the antigen rather than

to specific type sensitization in the patient. None of these three patients gave a specific reaction with any of the other antigens used.

Deducting these three reactions from Table 1, we may reconstruct it as follows:

TABLE 2

Type of Pneumonia	Number of Cases Tested	Number Showing Specific Type Reaction	Per Cent. Specific
I	47	5	10.6
II	9	1	11.1
III	8	1	12.5
IV	29	1	3.5

Although the number is small, it may be said that in these tests, no one of the fixed types of pneumonia shows any marked preponderance over the others as regards the ease with which intracutaneous reactions, specific for the type of infection, could be elicited.

The relation between the specific type reactions in Type I cases and treatment with specific antipneumococcus serum is shown in Table 3.

TABLE 3.—SPECIFIC TYPE REACTIONS AND SPECIFIC SERUM TREATMENT

Total of Type I pneumonias tested	47
Total of Type I pneumonias with specific reactions	6

Treated	Total Tested	Specific Reactions	Per Cent. Specific
With serum	20	2	10
Without serum	27	4	14.8

Thus, instead of finding more ease in eliciting this reaction following specific serum therapy, as might be expected from the report [11] of the earlier appearance of antibodies in such cases, a somewhat smaller proportion of these reactions appeared among cases so treated than among those receiving no serum.

Of the eleven cases showing specific type reactions, seven gave one such test with one or more negatives; three gave two with one or more negatives, and one gave three with one negative test. There was a total of sixteen specific type reactions out of thirty-seven performed on these eleven patients. The earliest specific test was performed on the sixth day of the disease, or the day of the termination of crisis; the latest was on the thirty-eighth day, or twenty-nine days after crisis. The only reaction of this kind obtained before crisis was on the eighth day of the disease, or three days before crisis. This, however, was not specific for the type of organism found in the patient's sputum. Dividing the disease into weekly periods, the specific type reaction occurs as shown in Table 4.

11. Knox, J. H., Moss, W. L. and Brown G. L.: J. Exper. M. **12**:562, 1910.

TABLE 4

Week	1st	2d	3d	4th	5th	6th
Of the disease	1	6	3	2	3	1
After crisis	7	1	4	1	1	

One reaction occurred before and one during crisis. Thus the largest number of these reactions appeared during the second week of the disease or the first week after crisis. With the crisis a phenomenon of allergy, this is what would be expected since the seven to fourteen day interval is that commonly required for antibody formation (vaccinia [12] and serum disease [13]) after which period there is a gradual reduction in the concentration of antibodies, and since directly after the clinical manifestation, the antibodies may be in their highest concentration,[14] as it is on these antibodies that the antigen must depend for its reaction.

In these eleven cases the various antigens were used as shown in Table 5.

TABLE 5

Number of antigen	1	2	3	4	Ic	5	6	7	8	9	10
Total tests	4	5	3	4	3	6	2	3	1	4	4
Specific tests	0	5	0	3	1	2	1	1	0	3	0

It will be remembered that Antigens 2, 4, 5 and 7 were identical with Antigens 1, 3 and 6, respectively, except that the former were autolyzed in the incubator for a week or more, while the latter were put directly on ice. Thus out of eighteen tests with autolyzed antigens, eleven (61.1 per cent.) gave specific type reactions; while out of nine tests with nonautolyzed antigens only one (11.1 per cent.) so reacted. The superiority of the former type of antigen is well illustrated in Case 11 in which autolyzed antigens gave specific type reactions on the thirteenth and twenty-ninth days, and no such reaction on the twenty-third day. It is very unlikely that in the interval of sixteen days between the positive tests, the patient lost his specific type sensitiveness and regained it again, but rather that the antigen used during this interval was not suitable to elicit such a reaction. In this connection, it is significant that when one case responded specifically on the thirty-eighth day of the disease to an autolyzed antigen of culture I C

12. Rosenau, M. J.: Preventive Medicine and Hygiene, New York., D. Appleton & Co., 1918.

13. Von Pirquet, C., and Schick, B.: Die Serumkrankheit, Leipsig, Deuticke, 1905.

14. Chickering, H. T.: J. Exper M. **20**:599, 1914. Dochez, A. R.: J. Exper. M. **16**:655, 1912. Ricketts, H. T.: Infection, Immunity and Serum Therapy. Chicago, A. M. A. Press, 1906. Rosenow, E. C.: J. Infect. Dis. **3**:683, 1906. Tunnicliff, R.: J. Infect. Dis. **8**:302, 1911. Wolf, H. E.: J. Infect. Dis. **3**:731, 1906.

(homologous) the identically prepared, but nonautolyzed, antigen gave no reaction.

Of the antigens in which the pneumococci were subjected to considerable violence (Antigens 8, 9 and 10) No. 9 was the only one showing any reaction to a single type and the lack of type specificity of these reactions has already been discussed.

In the light of Weil's [2] work, the common reactions are especially worthy of analysis. Of the 104 cases of lobar pneumonia tested, forty-six (42.3 per cent.) showed the reaction with one or more antigens, and of the twenty controls, nine (45 per cent.) showed such reactions. They were elicited by the various antigens as shown in Table 6.

TABLE 6

Antigens	1	2	3	4	5	6	7	8	9	10
Reactions in pneumonias	5	4	6	7	3	2	0	2	7	17
Reactions in controls	1	3	0	1	0	2	0	2	0	3

The earliest reaction of this type appeared on the sixth day of the disease and the latest on the forty-sixth day. In relation to crisis, one appeared twenty-four hours before, two during, and the remainder after crisis.

These reactions were at their height in eighteen hours, and were fading in from twenty-four to thirty-six hours. They showed no differentiation between central induration and areola. Though a central macule, sometimes just palpable about the point of inoculation, might persist for forty-eight hours or even longer, there was no pigmentation or scaling. Weil describes what he considers a positive reaction to the pneumococcus protein as follows:

> Within the twenty hours following the injection further changes may occur at the site of injection. A fairly well circumscribed area of erythema, with slight infiltration and elevation of the skin surrounding the point of puncture, may develop. If the infiltration is marked, a true papule results. These changes may persist for forty-eight hours or more. . . . The normal individuals, or the diseased controls, may or may not present a reaction, depending presumably on their previous sensitization by the pneumococcus or an allied organism.

It would seem, then, that the reactions obtained by Weil and those described here as common reactions were the same. Weil is not disturbed by similar reactions in controls and feels that they are specific for the pneumococcus protein. When a history of lobar pneumonia cannot be obtained, he feels that an abortive and unrecognized attack may be used as an explanation of sensitization. Another explanation is that suggested by Gay [9] for his "meningococcin" reaction in normals with negative cultures, namely, that the presence of the organisms on the mucous membrane in the past was sufficient to

sensitize. It is impossible to check up Gay's suggestion, because the discovery of a carrier state in the past is beyond present day bacteriologic technic. At least, it can be said that a test in which 45 per cent. of the controls react is of no service diagnostically.

SUMMARY

Of 104 cases of lobar pneumonia, eleven (10.5 per cent.) gave one or more intracutaneous reactions to only one type of pneumococcus used, while forty-six (42.3 per cent.) reacted to two or more types. Of twenty controls none showed the single type reaction, while nine (45 per cent.) showed the multiple type reactions.

These two reactions are sharply differentiated both as to time and character. The reactions elicited to a single type of pneumococcus were (with the exception of those from Antigen 9) specific for the type of organism isolated from the patient. The reactions, elicited by multiple types of pneumococci in 42.3 per cent. of the cases of lobar pneumonia and in 45 per cent. of the controls were not specific for the type of pneumococcus causing the disease. To determine whether they are specific for pneumococcus protein or not a control antigen made from other bacteria should be used.

In 10 per cent. of the cases treated with Type I antipneumococcus serum, specific type reactions were obtained, and in 14.8 per cent. not so treated there were similar reactions. No one of the fixed types showed any marked preponderance of specific type reactions. The longest period over which the specific type reaction was obtained was seventeen days. The largest number of the specific type reactions occurred during the second week of the disease (six cases) and the first week after crisis (seven cases).

With antigens prepared from simple saline suspensions of pneumococci, 61.1 per cent. of the tests, performed on the patients showing the specific type reactions, were positive when the antigen used had been autolyzed in the incubator for a week or more, and 11.1 per cent. of the tests with nonautolyzed antigen were positive.

Of the antigens in which the pneumococci were treated with bile, alcohol, etc., only one gave reactions to a single type and these were probably all nonspecific for the type of infection present.

No reactions comparable to those reported by Weiss and Kolmer with their "pneumotoxin" were obtained with a similar preparation, nor was there any specific absence of reactions as might be expected from an analogy to the Schick test.

CONCLUSIONS

1. Intracutaneous reactions specific for the type of pneumococcus causing lobar pneumonia may be obtained in certain cases.

2. The reaction has not been demonstrated sufficiently early to be of service in directing specific serum therapy.

3. The largest number of reactions occur during the period when, on the assumption of allergy, the highest concentration of antibodies would be expected.

4. The sensitization responsible for the specific reactions may persist more than two weeks.

5. The most satisfactory antigen for obtaining specific type reactions is made by autolyzing saline solution or distilled water suspensions of the various types of pneumococci.

6. A reaction, differing from that which is specific for type in time and character, may be obtained in a considerable number of cases of lobar pneumonia and controls. This appears with more than one of the pneumococcus type antigens and is in no way specific for the type of organism causing the infection. Whether this reaction is specific for a common factor in all types of pneumococcus protein or whether it is in no way specific for the organisms composing the antigens has not been demonstrated.

CLINICAL STUDIES ON THE RESPIRATION

VIII. THE RELATION OF DYSPNEA TO THE MAXIMUM MINUTE-VOLUME OF PULMONARY VENTILATION *

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Failure to obtain the required amount of oxygen or to remove a sufficient quantity of carbon dioxid from the body tissues results in the subjective sensation of dyspnea. The maintenance of a gaseous exchange which is adequate for the needs of the metabolism depends on the coordination of several factors, and insufficiency of any one of these may produce dyspnea, but we proposed here to consider only the subject of the pulmonary ventilation. With the body at complete rest the demand for oxygen is supplied and the excess carbon dioxid is removed when an individual is breathing from 4 to 5 liters of air per minute. Physical exertion requires a greater gaseous exchange and this is met by an increase in the amount of air breathed which is nearly proportional to the rise in metabolism. The degree, therefore, to which the metabolism may be increased by physical exertion without the production of dyspnea will depend, in part at least, on the ability to increase the minute-volume of the respiration so that it keeps pace with the metabolism. Aside from any other factors, the maximum minute-volume which an individual is capable of maintaining thus sets a definite limit to the amount of exercise which he can carry on without dyspnea, and the determination of the maximum minute-volume becomes a point of considerable practical interest. The maximum minute-volume depends, of course, on the ability to increase the rate, and more especially the depth, of breathing, and it is normally subject to variations depending on such factors as the vital capacity of the lungs and physical training, while in pathologic conditions it may be affected by numerous influences. The difference between the amount of air breathed per minute when lying quietly at rest and the amount breathed during the greatest exertion, or the maximum minute-volume, constitutes the pulmonary reserve which enables an individual to provide a greater supply of oxygen and remove larger quantities of

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carbon dioxid from the body when the demand is made. An individual with a large pulmonary reserve may be capable of violent exercise without dyspnea, while a patient with a very small reserve, from any cause, as, for instance, from heart disease, will become dyspneic on slight exertion. Hence the tendency to dyspnea depends, in part at least, on the extent of the pulmonary reserve.

The first experiments to be reported consist of an attempt to determine the maximum minute-volume and the pulmonary reserve in normal young men. The second series of experiments was devised to illustrate the effect on the pulmonary reserve of a decrease in the vital capacity of the lungs, with a consequent diminution of the maximum minute-volume.

THE MAXIMUM MINUTE-VOLUME IN NORMAL YOUNG MEN

To determine the maximum minute-volume which can be maintained during exercise, a study was made of twelve normal, young, male adults. The volume of air breathed was measured by conducting the expired air through a Bohr meter while the subject was riding on a stationary bicycle. During the period of exercise, the subject was instructed to ride hard until he was exhausted, and toward the end of the experiment he was encouraged to "spurt" for thirty seconds. The duration of the experiment varied from two and one-half to fifteen minutes, depending on the endurance of the individual. Dyspnea and muscular fatigue were both factors in making the subject stop riding and it was often difficult to determine which was the more important.

The results of the experiments, which are summarized in Table 1, show that in the twelve normal subjects the average minute-volume during the last one and one-half minutes of the observation, when the exercise was most violent was 60.3 liters. For periods of thirty seconds somewhat higher minute-volumes were often obtained, but these were maintained for so short a time that they are of less practical significance from the present point of view. No observations were made on the minute-volume of these subjects when lying down at complete rest, but general experience indicates that the average would not be far from 5 liters per minute. On this basis, it is clear that the pulmonary reserve is such that the minute-volume during violent exercise may be raised to about twelve times its resting value.

It is of interest to analyze the high minute-volumes in order to find out how they have been produced. There is always an increase in the rate of respiration and this consists of an average rise to 34 per minute during severe exercise. During the last minute and one-half of exercise the lowest rate observed was 26 and the highest 45 per minute, but in eight of the twelve subjects the rate was between 31 and 37. It would appear, therefore, that a rate of respiration of about 35 per

minute is usually attained during severe exertion. The other factor in producing the high minute-volume breathed during exercise is the increase in the depth of respiration. The depth of breathing will, of course, be governed to some extent by the vital capacity of the lungs, but it is quite obvious that when breathing rapidly it is impossible for the volume of each respiration to be equal to the total volume of the vital capacity. In the subjects investigated it was found that the volume of each respiration, during the period when they were breathing their maximum minute-volume, varied between 23 per cent. and 45 per cent. of their vital capacity, with nine of the twelve subjects using between 27 and 39 per cent. In general, therefore, an average of about 33 per cent. of the vital capacity was made use of with each respiration during the period of greatest exertion. It is interesting

TABLE 1.—SUMMARY OF EXPERIMENTS ON TWELVE SUBJECTS

No.	Subject	Vital Capacity, C.c.	Highest Minute-Volume for 30 Seconds, Liters	Duration of Exercise, Min.	Pulmonary Ventilation for Last 1½ Minutes of Exercise			Percentage of Vital Capacity per Respiration
					Minute-Volume, Liters	Respiratory Rate	Volume per Respiration, C.c.	
1	G. E. H.	7,180	84.00	7	79.0	39	2,050	28
2	A. M. G.	6,200	67.2	4	60.8	26	2,329	38
3	K. T. R.	5,530	60.4	5	58.9	31	1,900	34
4	J. B. M.	5,000	60.0	2½	50.0	37	1,367	27
5	T. E. B.	5,180	63.0	8	58.7	37	1,586	31
6	W. C. R.	5,400	66.0	6½	56.6	45	1,258	23
7	F. C. H.	5,530	84.6	12	80.0	35	2,285	41
8	J. W.	5,080	74.0	15	69.5	35	1,985	39
9	B. C. D.	5,210	54.6	4½	52.6	37	1,422	27
10	W. T. V.	5,180	50.4	5½	47.6	27	1,762	34
11	J. M. Mc.	4,210	60.4	7½	60.6	32	1,895	45
12	F. B. B.	5,080	50.6	8	48.2	31	1,555	31
	Average	.....	60.3	...	....	34	.....	33

that Barr and Peters[1] found that normal subjects and patients with heart disease, made dyspneic by rebreathing carbon dioxid, were able to use between one-third and one-half the volume of their vital capacity at each respiration. If one accepts the usual figures associated with the maximum minute-volume in this group of subjects, of a rate of 35 per minute and a volume per respiration equal to 33 per cent. of the vital capacity, it is possible to compute with fair approximation the theoretical maximum minute-volume of any individual if the vital capacity is known. Thus, if the vital capacity is 4.600 c.c., the maximum minute-volume is $\frac{4600}{3} \times 35$, or 53.7 liters. Figures obtained in such a manner, have, of course, only a relative value, and there will necessarily be considerable individual variation from such theoretically derived maximum minute-volumes depending on the extent to which the individual under consideration is able to increase the rate and depth of

1. Barr, D. P., and Peters, J. P., Jr.: Am. J. Physiol. **54**:345, 1920.

respiration. If the above formula be applied to the twelve subjects of these observations, it is found that the actual minute-volume of air breathed during the minute and one-half of greatest exertion was between 79 and 129 per cent. of the calculated maximum minute-volume, but in nine of the twelve subjects it was between 79 and 98 per cent. of the calculated maximum. The average minute-volume of the twelve subjects is 96 per cent. of the calculated maximum. Accepting the fact, therefore, that such calculations can give only a rough approximation of the truth, it is nevertheless clear that by their use it is possible to determine, with a degree of error that is unimportant for practical purposes, the maximum minute-volume of respiration which any individual can maintain, if the vital capacity of the lungs is known. Since most persons are able to increase the rate of respiration to about 35 per minute, or to the usual maximum rate during severe exertion, it is obvious that the fundamental factor which influences the maximum minute-volume is the vital capacity of the lungs. The clinical significance of these observations will be discussed later.

THE EFFECT OF REDUCTION OF VITAL CAPACITY OF THE LUNGS ON THE MAXIMUM MINUTE-VOLUME OF PULMONARY VENTILATION AND ON THE PRODUCTION OF DYSPNEA

The above observations having called attention to the importance of the maximum minute-volume of the respiration in its relation to bodily activity and the production of dyspnea, and also to the importance of the vital capacity of the lungs in determining the maximum minute-volume, the experiments to be described now were devised as an attempt to illustrate the relation of variations in the vital capacity of the lungs to the production of dyspnea.

It was found possible to cause an artificial reduction of the vital capacity to about one-half the normal value by means of a heavy canvas swathe strapped tightly round the chest, and in two healthy subjects the reaction to exercise was studied both before and after reducing the vital capacity in this way. Observations were made during the fasting state, on the respiration rate, volume per respiration, minute-volume, oxygen consumption, and carbon dioxid production per minute while the subject was lying at complete rest (Period I), standing at rest (Period II), walking sixty steps upstairs on a treadmill in sixty seconds (Period III), and over two consecutive five-minute periods standing at rest immediately after the walk (Periods IV and V). The amount of exercise involved in the walk upstairs was, of course, slight and caused little shortness of breath. In order to increase the exertion and produce more dyspnea a pack weighing 50 pounds was then put on the subject's back and he again walked sixty steps upstairs in sixty seconds (Period VI), this exercise being immediately followed by two five-

minute periods of observation while standing at rest (Periods VII and VIII). In each experiment the subject had been fasting fourteen hours so that the effect of food on the metabolism was eliminated. The expired air was collected in two 100 liter Tissot spirometers by means of a half-mask fitting tightly over the nose and mouth and connected to the spirometers with rubber tubing of large caliber. The oxygen and carbon dioxid percentages in the expired air were determined by analysis with the Haldane gas analysis apparatus. Duplicate analyses

TABLE 2.—SUMMARY OF EXPERIMENTS ON SUBJECT S. G.

Subject, S. G.: Age, 24 years; weight, 68.9 kg.; height, 171.4 cm.; surface area, 1.80 sq. m.

Experiment A: Vital Capacity = 4,600 C.c.

$$\text{Maximum Minute-Volume} = \frac{\text{V. C.}}{2} \times 35 = 53.7 \text{ liters.}$$

Period	Respiratory Rate	Volume per Respiration		Minute-Volume		Oxygen Consumption, C.c. per Minute	CO_2 Production, C.c. per Minute
		C.c.	Percentage of Vital Capacity	Liters	Percentage of Maximum Minute-Volume		
I. Basal	8.9	500	9	4.45	8	241	189
II. Standing at rest 5 minutes	11.2	503	12	6.30	12	278	227
III. Walking 60 steps	19.0	750	16	14.30	27 no dyspnea	794	587
IV. Rest of 5 min.	11.4	765	16	8.74	16	428	358
V. Rest of 5 min.	11.5	537	12	6.35	12	261	222
VI. Walking 60 steps carrying 50 pound pack	23.0	792	17	18.20	34 slight dyspnea	973	744
VII. Rest of 5 min.	13.0	1,120	24	14.56	27	655	629
VIII. Rest of 5 min.	13.0	540	12	7.04	13	271	238

Experiment B. Vital Capacity = 2,100 C.c.

$$\text{Maximum Minute-Volume} = \frac{\text{V. C.}}{3} \times 35 = 24.5 \text{ liters.}$$

I. Basal	16.9	358	17	6.15	25	250	201
II. Standing at rest 5 minutes	19.3	386	18	7.44	30	281	225
III. Walking 60 steps	28.0	560	27	15.70	64 moderate dyspnea	836	571
IV. Rest of 5 min.	26.2	515	24	13.50	55	558	452
V. Rest of 5 min.	23.1	425	21	10.00	41	348	304
VI. Walking 60 steps carrying 50 pound pack	28.0	690	33	19.50	80 more marked dyspnea	977	743
VII. Rest of 5 min.	21.0	705	34	14.80	60	566	489
VIII. Rest of 5 min.	20.3	490	23	9.83	40	277	276

were done on samples from each period and the results were not accepted unless they checked within 0.03 per cent. of the average for oxygen and 0.02 per cent. of the average for carbon dioxid. The respiratory rate was determined by means of a pneumograph leading to a tambour which recorded the respiratory movements by means of a lever marking on a smoked drum.

TABLE 3.—SUMMARY OF EXPERIMENTS ON SUBJECT F. F-S.

Subject, F. F-S.: Age, 25 years; weight, 72.1 kg.; height, 179.2 cm.; surface area, 1.90 sq. m.

Experiment A: Vital Capacity = 4,200 C.c.

$$\text{Maximum Minute-Volume} = \frac{\text{V. C.}}{3} \times 35 = 49 \text{ liters.}$$

Period	Respiratory Rate	Volume per Respiration		Minute-Volume		Oxygen Consumption, C.c. per Minute	CO_2 Production, C.c. per Minute
		C.c.	Percentage of Vital Capacity	Liters	Percentage of Maximum Minute-Volume		
I. Basal.....	11.8	313	7	3.69	8	202*	145
II. Standing at rest 5 minutes	14.0	420	10	5.87	12	240	202
III. Walking 60 steps	23.0	687	16	15.80	32 no dyspnea	976	717
IV. Rest of 5 min.	16.0	605	14	9.70	20	438	407
V. Rest of 5 min.	14.0	450	11	6.30	13	261	227
VI. Walking 60 steps carrying 50 pound pack	26.0	705	17	18.30	37 slight dyspnea	1110	859
VII. Rest of 5 min.	16.8	625	15	10.50	21	480	443
VIII. Rest of 5 min.	14.5	457	11	6.63	14	284	245

Experiment B: Vital Capacity = 2,550 C.c.†

$$\text{Maximum Minute-Volume} = \frac{\text{V. C.}}{3} \times 35 = 29.8 \text{ liters.}$$

I. Basal.....	18.4	302	11	5.57	18	224	186
II. Standing at rest 5 minutes	18.2	381	15	6.94	23	285	225
III. Walking 60 steps	31.0	610	24	18.90	64 moderate dyspnea	1090	752
IV. Rest of 5 min.	23.2	510	20	11.90	40	475	407
V. Rest of 5 min.	18.8	430	17	8.08	27	319	266
VI. Walking 60 steps carrying 50 pound pack	35.0	615	24	21.50	72 more marked dyspnea	1200	882
VII. Rest of 5 min.	27.8	530	21	14.70	50	540	518
VIII. Rest of 5 min.	22.4	375	15	8.40	28	309	248

* There was no apparent reason to account for this subject's abnormally low oxygen consumption. He was an active, alert, fourth year medical student with none of the signs or symptoms suggesting hypothyroidism. His basal metabolism on this occasion was —24 per cent. of normal when compared to the standards of DuBois.

† The vital capacity was 2,700 c.c. in the basal period. In periods II to VIII it was decreased to 2,550 c.c. by tightening the swathe. This alteration results in a theoretical maximum minute-volume of 31.5 liters in the basal period and 29.8 liters thereafter.

ANALYSIS OF RESULTS IN TABLES 2 AND 3

Tables 2 and 3 give the results of the two experiments. In both of them Experiment A was performed while the vital capacity was normal, while in Experiment B the vital capacity was reduced approximately 50 per cent. by means of the swathe. In Experiment A, Table 2, when the subject, S. G., was lying quietly at complete rest he was breathing 4.45 liters of air per minute. His maximum minute-volume, computed according to the formula suggested above, is 53.7 liters, so that during this first period he was breathing only 8 per cent. of his maximum minute-volume. In period III, while walking sixty steps in

sixty seconds, he breathed 14.30 liters per minute, or 27 per cent. of his maximum minute-volume and yet experienced no dyspnea. In Period VI, while walking sixty steps upstairs in a minute and carrying a 50 pound pack on his back, the minute-volume rose to 18.20 liters, or 34 per cent. of his maximum minute-volume and slight shortness of breath was noticed. In Experiment B, Table 2, the vital capacity of the lungs was reduced to 2,100 c.c. in the same subject and the calculated maximum minute-volume was thereby diminished to 24.5 liters. Under these conditions, although the subject was only breathing 6.15 liters per minute in Period I, while lying at complete rest, he was, nevertheless, using 25 per cent. of his maximum minute-volume. In Period III, when walking upstairs, he used 64 per cent. and was moderately dyspneic, and in Period VI, when walking upstairs with a pack, he used 80 per cent. of his maximum minute-volume and had marked dyspnea. In general, therefore, there is a striking correspondence between the degree of subjective dyspnea and the extent to which the maximum minute-volume is encroached upon. The actual minute-volumes in the corresponding exercise periods (Periods III and VI) in the experiments with and without the swathe were not very different but the degree of dyspnea was much greater in the experiment in which the vital capacity was reduced, Experiment B, and in which a larger proportion of the theoretical maximum minute-volume was made use of. Exactly the same relationships are found in the case of subject F. F-S. which are given in Table 3. Here, again, the subjective sensation of dyspnea varied, not with the actual minute-volume breathed, but with the extent of utilization of the maximum minute volume or, to express it in another way, with the decrease in the pulmonary reserve.

In both sets of observations shown in Tables 2 and 3 the oxygen consumption was approximately the same in the corresponding periods of Experiments A and B. There is a general tendency to a slightly higher metabolism in the experiments with reduced vital capacity and this is probably due largely to the discomfort incident to the very tight swathe and to the greater exertion associated with more rapid breathing. The minute-volumes for the corresponding periods are almost uniformly higher in the experiments with reduced vital capacity. This depends on the fact that in order to obtain the volume of alveolar ventilation necessary to meet the needs of the metabolism it was easier to increase the rate of respiration than it was to increase the depth. Under such circumstances the "dead space" of the upper respiratory tract becomes an important factor and the total minute-volume of pulmonary ventilation must be increased in order to produce the same volume of alveolar ventilation.

DISCUSSION

The first observations described were made on twelve normal young men who rode on a stationary bicycle until they were forced to stop on account of complete exhaustion. During the last one and one-half minutes of the ride, when the exercise was most violent and the dyspnea great, the average minute-volume of air breathed was 60.5 liters, or approximately twelve times the average minute-volume of such a group of men when they are lying down at complete rest. These figures give a general indication of the normal pulmonary reserve, by virtue of which the individual is able to increase the pulmonary ventilation and keep it adequate to the needs of the body when the metabolism is raised far above its resting or basal value by severe exercise. An analysis of these high minute-volumes shows that they were obtained by increasing the rate of respiration up to an average maximum of about 35 per minute, and by increasing the depth of each respiration up to a volume which approximates one third of the vital capacity of the lungs. On this basis, it was suggested that the maximum minute-volume which can be maintained for more than a very short period can be calculated in any given instance with an accuracy which is sufficient for practical purposes, by multiplying one-third of the vital capacity of the lungs by 35. Such a calculated or theoretic maximum minute-volume has considerable clinical significance for it tells about how far the person concerned is able to increase his minute-volume, and consequently how great an increase of metabolism he can meet with a pulmonary ventilation which will ensure proper aeration of the blood in the lungs. If the minute-volume of respiration can only be raised to three times the volume that a given subject breathes while at rest, then he will not be able to meet much more than a three-fold increase of metabolism, and he will become dyspneic walking slowly upstairs, but if the minute-volume can be raised to six or seven times above the resting value then the subject will be able to carry on most of the activities of a normal life without subjective dyspnea. The maximum minute-volume calculated in this manner is thus a guide to the amount of physical exertion that any individual may be expected to undertake.

The maximum minute-volume that a person can breathe depends on the rate and depth of the respiration. The observations reported appear to show that the highest rate that is compatible with efficient respiration is about 35 per minute, and practical experience indicates that most persons, whether or not they are in normal condition, can raise their respiration rate to this figure. The important factor in producing variations in the maximum minute-volume is thus the vital capacity of the lungs, which determines the possible depth of breathing. This

is, of course, subject to marked changes in normal, and to a greater extent in pathological conditions.

In the second series of observations reported, two subjects were studied while walking upstairs on a treadmill. One set of experiments on each of them was carried out in the normal state, and one set when the vital capacity was reduced to about one-half by means of a tight chest swathe. The wholly artificial condition this produced is not unlike that in a case of pleurisy with effusion and simulates in some degree other conditions, such as heart disease, in which the vital capacity of the lungs is below normal. The calculated maximum minute-volume was, of course, much less in the experiments with the chest swathe than in those in which the vital capacity was normal and it was found that the tendency to dyspnea varied closely with the percentage of the calculated maximum minute-volume that was being used in respiration. When the minute-volume breathed was only 25 per cent. of the maximum, the subject was not conscious of his respiration; when it was 50 per cent. he noticed that he was breathing deeply, and when it was 75 per cent. of the maximum he was frankly short of breath. These experiments, therefore, are of interest in that they bring out the importance of the conception of the maximum minute-volume of the pulmonary ventilation as one of the factors which determine the occurrence of dyspnea in various clinical conditions. This factor can be easily expressed in a sufficiently accurate quantitative manner and it has a broader physiologic significance than has the determination of the vital capacity of the lungs alone, for the minute-volume of pulmonary ventilation bears a close relationship to those fundamental processes of the body which go to make up what is known as the metabolism. The essential cause of the variations which may occur in the maximum minute-volume is an alteration in the vital capacity of the lungs and this may, therefore, be regarded as a practical index of the maximum minute-volume.

POSITION AND ACTIVITIES OF THE DIAPHRAGM AS AFFECTED BY CHANGES OF POSTURE *

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Most studies of the diaphragm are made with the subject standing, sitting or lying prone or supine. Such consideration ignores the fact that in health, as well as in disease, much time is spent lying on the side, and that the position and activities of this muscle and adjoining organs are greatly changed by shifts of posture. Although the literature is not without more or less detailed reference to these changes, their magnitude and clinical importance are popularly underestimated. As they affect directly physical signs, and as convenience or necessity frequently demands examination of a patient lying on one or the other side, it follows that an understanding of the action of the diaphragm in lateral positions of recumbency possesses an interest of practical value.

The relaxed diaphragm, in health, assumes a height and position dependent on forces exerted from below as well as from above. Recumbent on the back or face, gravity operates on the viscera in such a direction as to affect the diaphragm least. In this position the organ arches high into the chest. When standing or sitting, gravity comes into action on the thoracic organs above and the abdominal viscera below in such a manner as to push and draw the diaphragm downward. Its level is lower in the sitting position because of relaxed abdominal walls and consequent opportunity offered the viscera to sag forward as well as downward.

While a number of normal subjects form the basis of this discussion, in order to reduce the problem to its simplest terms, effort has been made to present an average specimen. Such a process is not without acknowledged error, in that wide variations from a so-called average present themselves. However, as variations in different types, in respect to the points under discussion, are of degree rather than kind, the error is not of a serious nature.

In our studies of normal chests, a fixed point, arbitrarily selected on the first lumbar vertebra, has been utilized. Variations in height of the diaphragm are measured on a line drawn from this point parallel

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to the vertebral column. In a state of normal inspiration, the distances above the marker of the right and left domes respectively are:

Standing: 6.5 and 5 cm.
Sitting: 5.5 and 3 cm.
Prone on abdomen: 12 and 9 cm.

It is thus seen that the right dome is 5.5 cm. and the left dome 6 cm. higher when the subject is reclining than when he is sitting. In all three positions, the excursion during normal, mixed breathing is about equal on the two sides and varies from 1.5 to 2.5 cm. in extent.

With assumption of the right prone position, the upper or left leaf of the diaphragm descends, opening to a considerable extent the left costophrenic angle, while the dependent or right leaf takes a higher level, at the same time increasing the extent of costophrenic contact. During quiet breathing, the excursion of the dependent half of the muscle is greater than that of the upper, the ratio being approximately 2 to 1. Recumbency on the left side reverses conditions, the right half of the diaphragm assuming a lower level, and exhibiting less excursion than the dependent left half. The explanation of these changes is simple on a purely mechanical basis. Both thoracic and abdominal viscera, especially the latter, because of their great weight and mobility, sag toward the dependent side, thus opening the upper costophrenic angle and straightening the upper diaphragm. In this position, the effect of equal contraction of the halves of the muscle will differ on the two sides. The dependent half, being highly arched, will descend, whereas the upper, approaching more nearly a plane, will tend rather to antagonize the intercostal muscles. In other words, the upper half works to a better mechanical, but poorer respiratory advantage than does the dependent half.

NEIGHBORING ORGANS

The effects of lateral recumbency on the positions and activities of adjacent organs are manifold. However, we here confine our remarks to three, namely: (1) the position of the heart; (2) marginal sounds or râles; (3) breath sounds at the bases.

1. The Heart.—In all positions the roentgenograms on which our results are based were taken at a distance of five feet from the plate. By actual measurements the dimensions of the negative do not vary more than 1 cm. from those of the subject, so that errors in detail are comparatively slight. The cardiac shifts in position are noted in figures which represent the distance of the apex from the midline of the spine. In some instances, the apex is near to or remote from the spine because of lateral tilting of the cardiac axis. In others, a

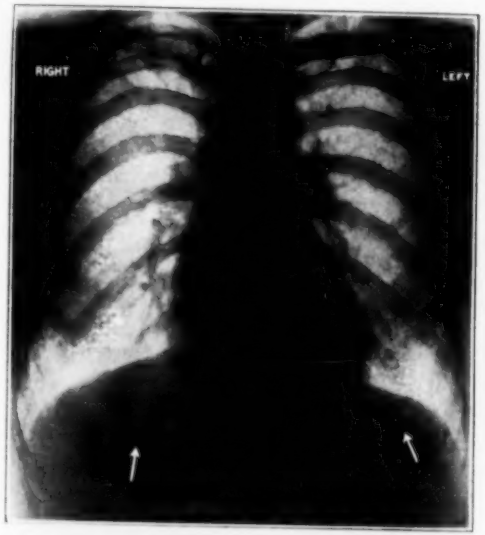

Fig. 1.—Subject sitting, end of normal inspiration, showing low position of diaphragm.

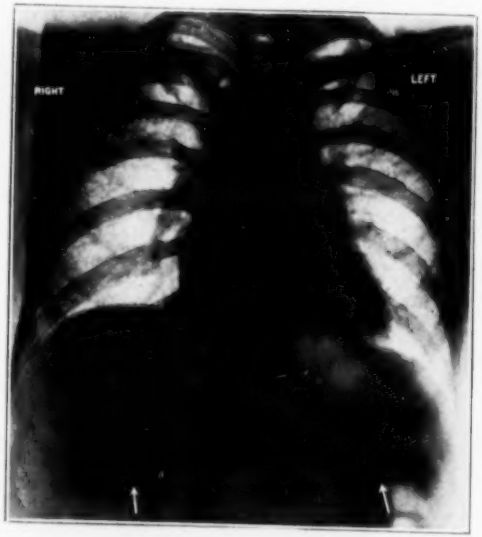

Fig. 2.—Same subject lying prone on abdomen, end of normal inspiration. Note high position of diaphragm.

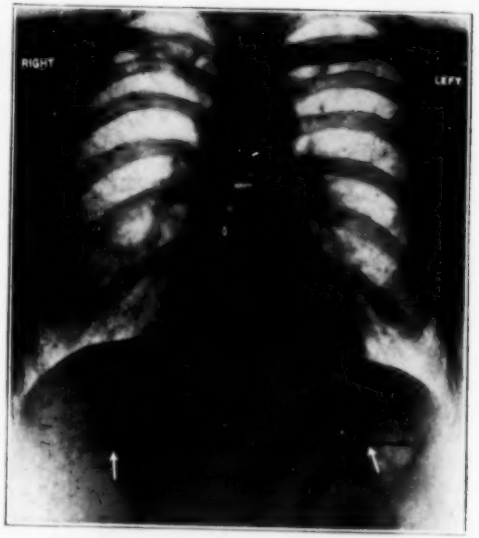

Fig. 3.—Same subject standing, showing position of diaphragm intermediate between Figs. 1 and 2.

Note: The "marker" shown in all of the photographs consists of a flexible wire, held in position by adhesive tape, at the level of the top of the first lumbar vertebra.

sagging mediastinum allows the entire cardia to fall toward the dependent side. Rotation is a third factor in the production of variations in heart shadow. Finally, two or more of these factors may be found combined.

The distance of the apex from the midline, in the average chest used for detailed illustration, in the sitting position is 8 cm.; prone on the abdomen, it is 10; both measurements taken at the end of a normal inspiration, a difference of 2 cm. effected by simple shift from a vertical to horizontal plane.

At the end of normal expiration, with the subject on the right side, the apex is 6 cm. from the midline. At the same respiratory phase, prone on the left, it is 12.3 cm., a total difference, allowing for slight error of oblique rays of about 6 cm. The difference in the same positions, at the end of full inspiration is much less marked, being only 1.5 cm. This is as one would naturally expect because of the firm pericardiophrenic attachment and the consequent straightening of the mediastinum incidental to descent of the diaphragm.

The distance of the left border of the heart from the midline at the end of normal inspiration, with the subject standing, is 8.5 cm., sitting, 8 cm.; prone on abdomen, 10 cm.; recumbent on the right side, 6.5 cm.; prone on left side, 11.7 cm. That is to say, with the ascension of the diaphragm consequent to a change from the vertical to horizontal position on the abdomen, the apex shifts to the left a distance of from 1.5 to 2 cm. Turning on the left side produces a further movement to the left of a little over 1.5 cm., while recumbency on the right side is accompanied by a shift to the right of 3.5 cm. The left border, then, in the right prone position, is only from 1.5 to 2 cm. to the right of the point which it occupied in the upright position, whereas prone on the left side it is removed from this point by a distance about twice as great. However, the subject having assumed a recumbent position may accomplish a greater cardiac shift by turning upon the right side than by turning to the left.

2. *Marginal Sounds.*—By the term marginal sounds we refer to that group of sounds which is heard over the base of the lung during deep inspiration. They vary in different individuals from dry crepitations or crackles to sounds resembling fine or medium size moist râles. Such sounds may be elicited in almost any normal individual capable of abdominal breathing. They are heard over the edge of descending lung and therefore assume the form of a wave rather than of a fixed line. The vertical length of this wave depends upon the extent of the complimental space and the ability of the individual to obliterate this space by diaphragmatic contraction. It is greatest in the axilla, tapering to a narrower area at the spine behind and ensiform cartilage in front.

Positions of recumbency are especially favorable to the production of marginal sounds because of the high position of the diaphragm and consequent increase in the complimental space. Right lateral recumbency further increasing the right complimental space, amplifies the extent of marginal sounds on the right side. At the same time, by opening the left space, this position diminishes or obliterates the sounds on the upper side. Reversal of position, reverses conditions. The sounds may be produced or dissipated at will by having the subject lie upon one or the other side.

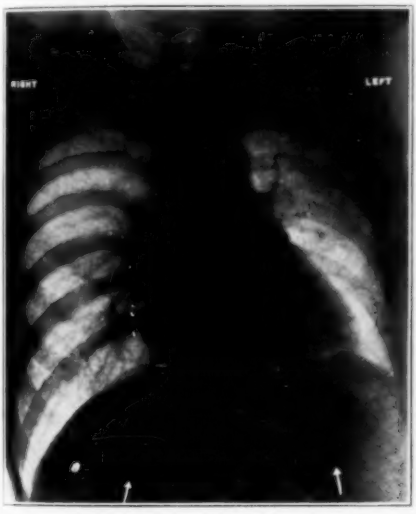

Fig. 4.—Prone on left side, end of normal expiration. Diaphragm high on left side, right costophrenic angle widely open, heart prolapsed far to left.

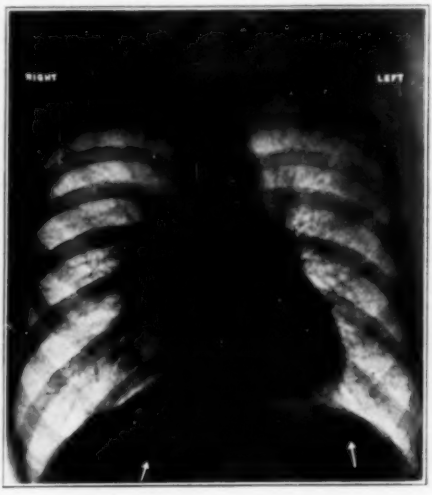

Fig. 5.—Same subject prone on left side, end of full inspiration. Diaphragm levels equal on two sides and heart occupying slight left position.

Note: Showing wide excursion of dependent left diaphragm and wide extent of separation from parietal pleura corresponding to area of marginal sounds on the dependent side. Note the change in axis of heart and position of apex.

(Because of the necessity for economy in reproduction of photographs, the illustrations in the corresponding respiratory phases with the subject prone on the right side, are omitted. Reversal of position, however, produces a corresponding reversal of position of the organs. With deep inspiration, there is a corresponding wide excursion of the dependent diaphragm, together with a cardiac shift toward the left.)

The tendency of an individual in deep breathing is always toward over inflation, so that after a number of inspirations the diaphragm becomes for awhile established at a lower level. Its excursion is thereby considerably curtailed and marginal sounds disappear, to recur

only after rest sufficient to permit the lung elasticity to reassert itself. This situation does not arise, or it may be obviated, when the subject instinctively, or as a result of instruction, forcibly exhales sufficiently to prevent over inflation.

In explaining the occurrence of marginal sounds, it is necessary to bear in mind the fact that at their point of audibility, three events are transpiring. The phrenic pleura is separating from the costal; the visceral pleura is gliding downward to replace the phrenic, and finally, air is entering the margins of the lungs.

That the second of these phenomena is not productive of marginal sounds may be assumed from the fact that viscerocostal friction is elsewhere inaudible in the chest. Moreover, marginal sounds are heard only during inspiration.

The view most generally accepted is based on inflation of the marginal air spaces, a theory dependent on complete or incomplete atalectasis of the lung. There are serious objections to such an explanation. In the first place, marginal sounds are heard in almost any normal subject capable of deep breathing. They may be repeatedly dissipated or produced at will by over inflation or strong deflation of the lung. They may likewise be made to appear and disappear by changes of position in lateral decubitus. Most convincing of all is the fact that they occur over a moving line keeping pace with Litten's Shadow and corresponding, not only to the downward moving margin of the lung, but also to the line of cleavage of the diaphragmatic from the parietal pleura.

Explanation for the production of marginal sounds based on separation of the phrenic from the parietal pleura is provided for in two ways. In the first place, other explanations, under close scrutiny, fail to withstand criticism. In the second place, the "peeling off" of the diaphragm from the costal pleura contributes a mechanism unique in pleural contact and, at least, theoretically satisfying. Further, it has been found that varying conditions of moisture and dryness of the pleural surfaces bear a direct relation to the quality and intensity of marginal sounds.

The points we wish to emphasize in connection with marginal râles are: (1) They may be elicited in the normal subject. (2) They are a tribute to the mobility of the diaphragm. (3) They are reversible in position and extent. (4) They are audible at the point of cleavage of the diaphragm from the chest wall and may therefore be heard early or late in deep inspiration according as one listens at the top or bottom of the costophrenic space.

3. Breath Sounds at the Bases.—Auscultation of the back from the seventh vertebra to the base, with the subject prone on the side,

reveals a more intense respiratory murmur on the dependent side. The difference is more marked in the expiratory than in the inspiratory phase. Relative intensification of breath sounds on the lower side is due to two factors; first, the more active ventilation of the lower part of this lung as revealed by the greater diaphragmatic excursion. In the second place, the relative compression and actual relaxation of the lower side furnish conditions favorable to better transmission of sound.

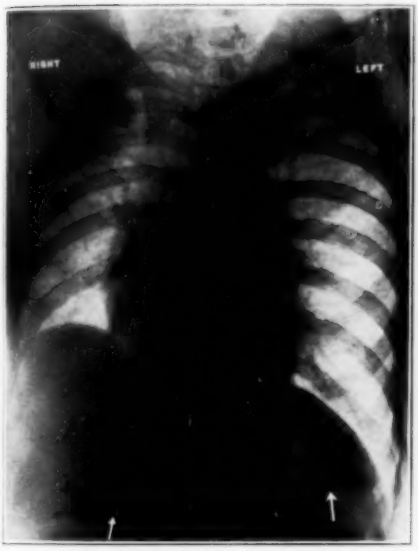

Fig. 6.—Subject prone on right side, end of normal inspiration. Showing high position of right dome of diaphragm, low position of left dome, also wide cardiac and mediastinal shadow to right of vertebral column.

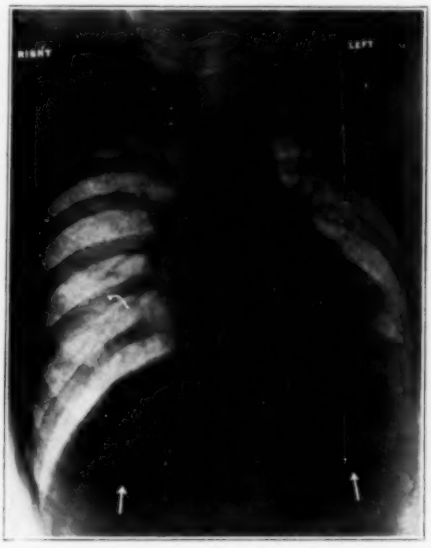

Fig. 7.—Same subject prone on left side, end of normal inspiration. Showing high position of left dome and low position of right. Little cardiac and mediastinal shadow seen to right of vertebral column.

Note the vast difference in levels of diaphragm and position of heart produced by turning from right to left prone position.

Inasmuch as the inspiratory murmur is produced close to the ear, while the expiratory sound is initiated at a point remote from the surface of the lung, it follows that in the inspiratory phase, ventilation is the more important agent, whereas in expiration, conduction probably plays a great rôle in augmenting sounds on the lower side. Accompanying intensification of the breath sounds just referred to, there is an increased intensity of the whispered sound, spoken word and of tactile fremitus.

SUMMARY

To summarize: The diaphragm is highest in the prone position; intermediate, with the subject standing erect; lowest in the sitting posture. Its excursion in these positions is equal on the two sides. Prone on the right side, the right dome is higher than the left and its excursion is in excess in the proportion of 2:1. Reversal of position, reverses the height and excursion of the two sides.

The position of the heart, accompanying changes in position of the diaphragm, is subject to a wide range. The extreme excursion is 6 cm.

Marginal sounds are heard over the healthy lung and are not incidental to or dependent upon pathology in the lung or pleura. They are heard over a broad area on the dependent side in lateral decubitus because of the greater extent of the complimental space. These sounds are heard best during vigorous inspiration following forceful expiration.

In lateral recumbency, the dependent lung is relatively relaxed. Its diaphragmatic ventilation is in excess of that of the upper lung. Breath, voice and whisper sounds and tactile fremitus are all increased as compared with the opposite side.[1]

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1. Bushnell, George E.: Some Extra Pulmonary Sounds Which Simulate Râles, Med. Rec. (Jan. 20) 1912, Vol. 81, Page 101-107 inc.; Marginal Sounds in the Diagnosis of Pulmonary Tuberculosis, Med. Rec. (Dec. 21) 1912, Vol. 82, Page 1109.

Gerhardt: Auskultation und Perkussion.

Hoover, C. F.: The Functions of the Diaphragm and their Diagnostic Significance, Arch. Int. Med. **12**:214 (Aug.) 1913.

Morrison: Lancet **1**: (May 6) 1911. Page 1202.

AURICULOVENTRICULAR RHYTHM AND DIGITALIS*

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Auriculoventricular rhythm, a condition in which the A-V node assumes rhythmicity independent of the sinus node, is due to one of two causes; depressed irritability of the sinus node or enhanced irritability of the A-V node. Experimentally both types have been produced, the former by tying off (Engelmann [1]), injuring (Hering [2]), or cooling (Ganter and Zahn [3]) the sinus node, the latter by stimulating the A-V node either directly (Lohmann [4]) or through the left accelerator (Hering;[5] Rothberger and Winterberg [6]). Meek and Eyster [7] reviewed and extended the experimental work. By means of electrodes connected with a string galvanometer and applied direct to the heart they obtained evidence that in A-V rhythm the electrical activity originates in the A-V node.

Clinically, both types of the A-V rhythm have been observed, the type in which the irritability of the sinus node is depressed, characterized by a slow rhythm, and the type in which the irritability of the A-V node is enhanced, characterized by a relatively rapid rhythm. The former, though rare, is much the more common of the two. White [8] distinguishes further between A-V rhythm and simple ventricular escape. In the former the excitation wave arises from the A-V node alone, in the latter from both nodes simultaneously. He bases the distinction on the form of the P wave which is known to be inverted or upright according as the excitation wave arises near the A-V node or near the sinus node. A-V rhythm is, therefore, characterized by an inverted P wave, simple ventricular escape by an upright P wave. Of the two conditions A-V rhythm is much the more permanent.

The accompanying table indicates the variety of the conditions in which A-V rhythm occurs, together with the outcome of the cases. No death occurred as a result of A-V rhythm alone. In the fatal cases the postmortem examination revealed ample causes for death

* From the Cardiovascular Service of the Presbyterian Hospital.

1. Engelmann, Th. W.: Arch. f. Anat. u. Physiol. Physiol. Abth., 505, 1903.
2. Hering, H. E.: Arch. f. d. ges. Physiol. **136**:466, 1910.
3. Ganter, G., and Zahn, A.: Arch. f. d. ges. Physiol. **145**:335, 1912.
4. Lohmann, A.: Arch. f. Anat. u. Physiol., Physiol. Abth., 431, 1904.
5. Hering, H. E.: Zentralbl. f. physiol. **19**:129 (June) 1905.
6. Rothberger, C. J., and Winterberg, H.: Arch. f. d. ges. Physiol. **135**:559. 1910.
7. Meek, W. J., and Eyster, J. A. E.: Heart **5**:227, 1913.
8. White, P. D.: Arch. Int. Med. **18**:244 (Sept.) 1916.

quite apart from the A-V rhythm. In the other cases the arrhythmia was either transient or relatively short, with one exception, the case of Williams and James,[9] in which it was observed for fourteen months. During this period the patient improved. It is evident, therefore, that in and by itself A-V rhythm is not dangerous to life. When associated with severe infections or cardiac disease it is the associated disease which determines the prognosis.

The case reported here is of especial interest in view of its relation to digitalis. Such a relation has been reported but rarely. Norrie and Bastedo[10] observed it in a case of heart-block following the administration of digitalis. Cohn and Fraser,[11] also Cohn[12] give a clear description of A-V rhythm as an effect of digitalis. White[13] observed it in a case of auricular flutter in which the administration of digitalis was followed first, as expected, by auricular fibrillation and then by A-V rhythm instead of normal rhythm. Later[8] he recorded two cases of A-V rhythm following digitalis, the first a slow rhythm arising, in part at least, from depression of the sino-auricular node, the second a more rapid rhythm resulting from irritation of the A-V node. Egglestion[14] mentions A-V rhythm as one of the toxic effects of digitalis.

REPORT OF CASE

History.—A woman, aged 47, housewife, was first admitted to the Presbyterian Hospital, March 10, 1920. Her father and mother had died aged 35 and 25, respectively, and four of her brothers and sisters had died in infancy. Marital history included one miscarriage and two stillbirths. At the age of 18 she had an attack of acute arthritis in the left knee. Her symptoms began four weeks prior to admission and consisted of epigastric pain radiating to the left arm, dyspnea and edema.

Physical Examination.—This revealed cyanosis, emaciation and dyspnea. The heart was enlarged and a blowing systolic murmur was heard at the apex. Signs of a moderate amount of fluid in the right chest were present, together with congestion at the bases of the lungs. The liver was much enlarged and there was moderate edema. Blood pressure: 150/98. The roentgenogram showed a cardiac shadow extending 6 cm. to the right and 9.75 cm. to the left of the midline.

The blood Wassermann was negative. Blood urea was 0.78 gm. per liter; phthalein excretion, 19 per cent.

Clinical Diagnosis.—Chronic cardiac valvular disease; mitral insufficiency; cardiac insufficiency; caries of teeth.

Treatment.—She received 45 minims of the tincture of digitalis daily from March 17 to March 25.

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9. Williams, H. B., and James, H.: Heart **5**:109, 1913.
10. Norrie and Bastedo: St. Luke's Hospital, New York M. & S. Rep. No. 2, p. 101.
11. Cohn and Fraser: Internat. Med. Congr., Sec. 6, Pt. 2, p. 258, 1913.
12. Cohn, A. E.: J. A. M. A. **65**:1527 (Oct. 30) 1915.
13. White, P. D.: Arch. Int. Med. **16**:517 (Oct.) 1915.
14. Eggleston, Cary: Am. J. M. Sc. **160**:625, 1920.

Clinical Course.—She was readmitted May 12, 1920, after rapid return of decompensation. Physical signs were essentially the same, cardiac borders somewhat wider but liver not palpable. An irregularity of the pulse was noted. Blood pressure: systolic, 180; diastolic, 120. To the previous diagnosis were added hypertension and chronic nephritis. She was admitted for the third time September 3. For a while she improved gradually, but then developed ascites and was twice tapped. She died October 7 of pneumonia.

In taking the graphic records the galvanometer was standardized so that the introduction of 1 millivolt of current caused a deflection of the string 1 cm.

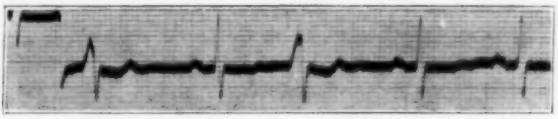

Fig. 1.—May 14, 1920. Lead I. Control record taken before administration of digitalis. Sequential rhythm. P-R interval 0.18. Rate = 80. Two ventricular extrasystoles recorded. Time, 1/25 sec.

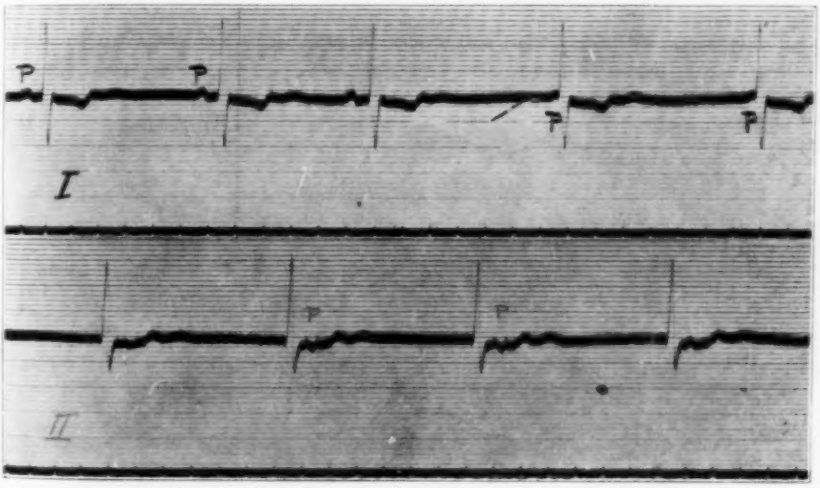

Fig. 2.—June 1, 1920. Lead I. Transition from sino-auricular to A-V rhythm. Lead II. A-V rhythm fully developed. P-R interval has changed from + 0.18 to — 0.18. Rate, 43.5.

The electrocardiograms taken on the first admission were essentially the same as shown in Figure 1. At this time the effect of digitalis was limited to minor changes in the T wave. On the second admission, the effect of digitalis was quite different. Figure 1 presents the control record taken on the third day. The P wave precedes the R wave

by a normal interval of 0.18 seconds, indicating a sequential rhythm, that is, one in which the pacemaker is located in the sinus node. P is of normal contour except that it is inverted in the third lead. The Q. R. S. complex is essentially normal except for a deep notch in Lead III. Frequent extra systoles occur. Digitalis was then given in the form of the tincture, 30 minims a day for five days, and 20 minims a day for two days. Figure 2 is the curve recorded just after cessation of digitalis. It is characterized by a marked bradycardia and a striking variability in the time relation of the P and R waves. Reading from left to right the P wave gradually approaches the R wave until it merges with it. This change is associated with a decrease in rate from 48 to 43. In Lead II the change of the position of P has continued until P appears after R. This wave is a clear example of auriculoventricular or nodal rhythm.

On the third admission no record was taken until after a course of digitalis consisting of 2 c. c. digifolin and 172 minims of the tincture in the course of eight days. This record (Fig. 3) shows essentially the same mechanism as Figure 2; bradycardia and A-V rhythm. Two days later only a single delayed nodal beat was recorded (Fig. 4); sequential rhythm otherwise present, though with a marked variation in shape and rate of P wave. One week later an occasional delayed nodal or A-V beat was recorded and two weeks later a reversion to a more rapid sequential rhythm with occasional extrosystoles of ventricular origin (Fig. 5).

There can be little doubt that the mechanism represented by Figures 2 and 3 is that of A-V rhythm. A possibility to be ruled out is A-V block with complete dissociation. In this case the auricular wave must appear sooner or later in the middle of diastole. This it failed to do in any of the several curves in which A-V rhythm was recorded. It is conceivable also that the abnormal P wave belongs to the following ventricular complex, in other words that there is a P-R interval of over a second. Such a delay in conduction without block is hardly probable.

The gradual transition from normal to A-V rhythm is puzzling. Two explanations have been advanced. According to the first the transition represents a stage during which both nodes are active. The auricle, receiving its stimulus from the sinus node, contracts in the normal way and its contraction is recorded as an upright P wave. The stimulus arising from the A-V node activates the ventricle prematurely. Hence the combination of an upright P wave and a diminished P-R interval. According to the second explanation the pace-maker simply migrates first to the auricular end of the A-V node and then gradually downward through this structure. As most of the delay in conduction takes place in the A-V node this migration is accompanied by all the

changes from positive to negative P-R interval. The auricle, receiving its stimulus from below, would be expected to contract in such a manner as to produce an inverted P wave. Ganter and Zahn [3] and Lewis [15] favor the former explanation, Hering,[2] Weil [16] and Meek and Eyster [7] the latter. In the present case the fact that the P wave remains upright throughout the transition tends to favor the hypothesis of an interference between two nodes, both active.

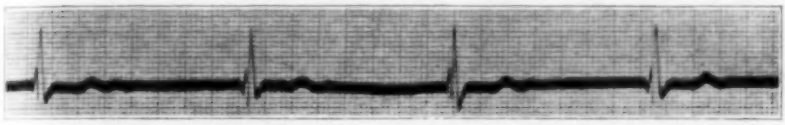

Fig. 3.—Sept. 14, 1920. Lead III. A-V rhythm. P wave merged with ventricular complex. Rate = 38.3.

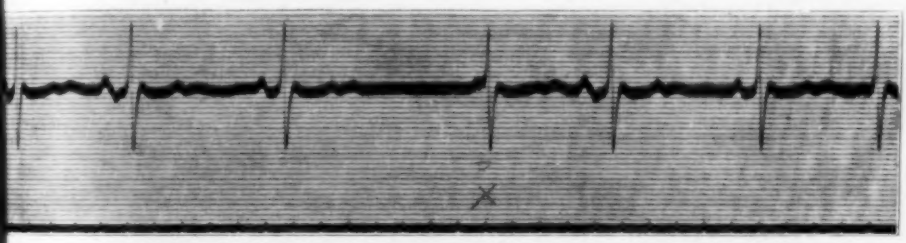

Fig. 4.—Sept. 16, 1920. Lead I. Delayed nodal beat at ×. Sinus arrhythmia. Unexplained variation is form of P wave. Rate = 53.9.

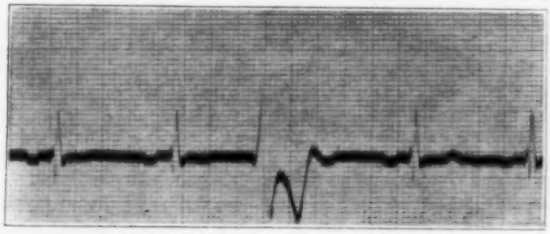

Fig. 5.—Sept. 28, 1920. Lead III. Sequential rhythm. Rate = 67.5. PR = 0.18. One ventricular extrasystole shown. (The inverted P wave was present in the third lead in all records and is of no apparent significance.)

Extracts from the Protocol of the Postmortem Examination.—Necropsy 9075; Dr. Von Glahn: Abdominal cavity 1,000 c.c. clear fluid.

Heart: The pericardial cavity does not contain an excess of fluid. The pericardium is slightly adherent to the anterior surface of the heart by delicate tendinous adhesions. There is a large tendinous patch on the anterior surface of the right ventricle and the vessels of the heart are engorged. The

15. Lewis, T.: Heart **5**:247, 1913.
16. Weil, A.: Deutsch. Arch. f. klin. med. **116**:486, 1914.

epicardium over the right auricle is roughened and the auricle is greatly distended. The heart weighs 420 gm. The right auricle contains postmortem clot and in the appendage and clinging to the wall of the auricle are antemortem thrombi. Just at the opening of the superior vena cava in the auricle the endocardium is quite thickened and opaque over an area about 2 cm. in its greatest diameter. There is also some thickening of the intima of the cava at this point. The foramen ovale is closed. The tricuspid valve shows a little thickening of the cusps but it is quite flexible. The columnae carnae stand out quite prominently. There are seen beneath the endocardium a few yellow areas which appear fatty. The pulmonic valve is thin and delicate. The left auricle contains only postmortem clot. The endocardium is slightly thickened over the entire auricle. The mitral valve leaflets are slightly thickened, but flexible. At the apex of the left ventricle are a few small grayish red thrombi which have softened centers. These are adherent to the wall of the ventricle, in the spaces between the columnae carnae. On the anterior and left posterior leaflets of the aortic valve are small clumps of gray translucent vegetations which break off readily. They are situated over the corpus aurantii. The coronary arteries show a few yellow fatty plaques, without calcification or obvious stenosis of the lumen. The myocardium is grayish red in color with here and there lighter areas due to connective tissue.

Anatomic Diagnosis.—Scars of endocardium of right auricle; cardiac hypertrophy; fibrous myocarditis; acute cardiac valvular disease, aortic; thrombi in right auricular appendage and left ventricle; chronic passive congestion of liver and spleen; ascites; chronic diffuse nephritis; confluent lobular pneumonia; acute fibrinous pleurisy; acute fibrinous pericarditis; arteriosclerosis, slight.

Microscopic Examination.—Serial sections of the sinus and A-V nodes together with the bundle of His and a portion of the branches were made and examined by myself. The sections were from 15 to 17 microns in thickness and every fifth one was examined. The sinus node was situated between superior and inferior vena cava, about 2 cm. from the orifice of the former. It was situated in a sulcus just beneath the endocardium. It measured 5.1 by 10 mm. and was about 1.5 mm. deep. The muscle cells of the node appeared normal. The connective tissue stroma comprised usually about one third, sometimes about one half of the nodal tissue. This amount does not appear in excess of normal. The arteries showed no sclerosis. Beneath the epicardium was a layer of fat infiltrated in the region of the node with cells of which a majority were lymphoid, the rest polymorphonuclear. The infiltration did not extend into the node. Microscopical examination of the sinus node therefore revealed no abnormality except a subendocardial infiltration which did not extend to the node itself.

The auriculoventricular node was found in the auricular tissue near the septal cusp of the mitral valve. It appeared normal as to condition of muscle fibers, arteries and proportion of connective tissue. Its greatest length was 17 mm., greatest width 7.5 mm., and depth 1 mm. The stem showed no abnormalities. The right and left branches were traced continuously to a point 10.5 mm. below the beginning of the node. No abnormalities were found.

As to the cause of the A-V rhythm, three possibilities must be considered: first, an organic lesion in the conduction system; second, an endogenous factor which failed to produce demonstrable pathologic lesions, and third, digitalis. The first was ruled out by the examination of serial sections. The second remains a possibility, though an unlikely one. Arrhythmias, heart block, for instance, can occur without digitalis or pathologic lesions, but the absence of the latter markedly diminishes the probability of an endogenous cause. In the third case, the relation

CLINICAL COURSE OF AURICULOVENTRICULAR RHYTHM

Observer	Diagnosis or Pathology	Outcome	Cause of Death
Belski (9)	(1) Acute rheumatic fever.....	Recovery	
	(2) Typhoid fever.....	Recovery, arrhythmia for 23 days	
	(3) Acute rheumatic fever.....	Lasted 1 day	
	(4) Scarlet fever.....	Recovery, arrhythmia lasted 4 weeks	
	(5) Acute rheumatic fever.....	lasted 2 days Recovery, arrhythmia	
Cowan, Fleming and Kennedy (10)	(1) Acute ulcerative endocarditis; profound inflammatory disturbance in A-V node	Died.....	Endocarditis; pneumonia
	(2) Acute endocarditis; acute inflammatory process involving A-V node	Died.....	Endocarditis
	(3) Acute endocarditis; subacute pericarditis; infiltration of A-V bundle and node	Died.....	Endocarditis; pericarditis
Williams and James (11)	Cardiac arrhythmia; A-V rhythm	Duration 1 year; improved	
Hume (12)	(1) Diphtheria, bronchopneumonia, pleural effusion; A-V node normal	Died.....	Diphtheria; bronchopneumonia; pleural effusion
	(2) Diphtheria, S-A node the seat of an acute inflammation	Died.....	Diphtheria
Weil (13)	(1) Carcinoma of stomach; pericarditis; arteriosclerosis of branch of coronary leading to region of sinus	Died.....	Carcinoma of stomach; pericarditis; arteriosclerosis
	(2) Syphilitic aortitis; thrombosis of left coronary artery	Died.....	Aortitis; aneurysm
	(3) Acute rheumatic fever.....	Discharged from hospital after 11 days	
White (15)	Auricular flutter; auricular fibrillation; A-V rhythm	Discharged from hospital 19 days after admission	
Laslett (15)	Malaise and pain in hip.....	Recovered after few days	
Neuhof (16)	Rheumatic fever.....	Left hospital after 12 days	
Fussell and Wolferth (17)	A-V rhythm; paroxysmal tachycardia	Died.....	Cardiac decompensation
Presbyterian Hospital 46985	Chronic myocarditis; cardiac insufficiency; cardiac arrhythmia; hypertension	Discharged improved after 5 weeks	
Presbyterian Hospital 45232	Acute rheumatic fever; acute rheumatic endocarditis; chronic cardiac valvular disease; mitral insufficiency and stenosis; A-V rhythm resulting in incomplete A-V dissociation with ventricular rate in excess of auricular	Discharged from hospital after 1 month, recovered from acute illness; electrocardiogram normal 1 month after discharge	

between the administration of digitalis and the onset of the A-V rhythm is so striking as to point with considerable emphasis to this last explanation. Electrocardiograms demonstrated sinus rhythm prior to a course of digitalis medication and A-V rhythm just after it; on another occasion A-V rhythm just after a course of digitalis and sinus rhythm after the effect had worn off. The clinical and pathologic observations combine to indicate a causal relation between digitalis and A-V rhythm.

In neither of our cases did stimulation or depression of the vagus nerve by pressure on the vagus nerve and atrophin, respectively, produce any definite effect. This is in accord with the findings of several other observers on the more permanent type of A-V rhythm, and would seem to indicate that the region affected lies within the heart rather than in the extrinsic cardiac nerves.[17]

SUMMARY

Auriculoventricular rhythm is not in itself fatal, but is frequently associated with severe infections or severe acute and chronic cardiac disease.

A case is described in which clinical and pathologic observations combined to indicate a causal relation between the administration of digitalis and auriculoventricular rhythm.

I wish to take the opportunity of expressing my thanks to Drs. T. Stuart Hart and Dr. Warfield T. Longcope for their helpful interest in the work, and to Miss Rose Richter for her advice and cooperation in the preparation of sections.

17. The following references also bear on this subject:
Belski, A.: Ztschr. f. klin. Med. **67**:515, 1909.
Cowan, J.; Fleming, G. B., and Kennedy, A. M.: Lancet **1**:277, 1912.
Hume, W. E.: Heart **5**:25, 1913.
Laslett, E. E.: Heart **6**:81, 1915.
Neuhof, S.: Arch. Int. Med. **15**:169 (Feb.) 1915.
Fussell, M. H., and Wolferth, C. C.: Arch. Int. Med. **26**:192 (Aug.) 1920.

A CASE OF DISSEMINATED MILIARY TUBERCULOSIS IN A STILL-BORN FETUS*

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Every layman knows that tuberculosis tends to cling to families. "The consumptive," says Hippocrates, "is born of a consumptive," and the search for an explanation of this fact has long engaged general interest. The earliest and most obvious explanation assumed an hereditary transmission, but the notion of an inherited tuberculosis, in a mendelian sense, could not, of course, survive the discovery of the cause of the disease. Other notions which have enjoyed more or less vogue at various times are, for example (*a*), germinal transmission by ovum or spermatozoon, such as is known to occur in silkworm pebrine. A certain amount of experimental evidence (which will be discussed in some detail later), supports this view, but the theory is open to criticism on various grounds, among others, that tuberculous infection of either germ cell would probably render it incapable of function, or, at least, lead to the early death of the embryo. (*b*) It is often said that the individual inherits not the disease itself, but a special predisposition to it. But this assumed predisposition has remained so vaguely defined as to represent little more than a form of words. If it is supposed to be a definite mendelian character, it is open to the same objection as the theory of hereditary transmission of the disease itself, and if it is assumed to be specific it runs counter to all we know about immunity; for immune bodies or toxins which might find their way from the maternal into the fetal circulation, would serve to protect the child, by conferring passive immunity or stimulating the production of an active immunity, respectively, unless, indeed, we are ready to believe that every infection is an anaphylactic phenomenon. Only if aggressins alone of the tubercle baccillus should be absorbed by the fetus would there be a specific lowering of resistance to the disease. These, being foreign substances, would tend to be eliminated very rapidly after birth. Moreover, the selective absorption of aggressins alone would probably be the rarest of occurrences. For example, Coca [1] found that anaphylactic sensitiveness is not inheritable in the true sense; but the mother may transmit specific antibodies from her blood to that of the fetus through the placenta. Krause [1a] observed

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1. Coca: J. Immunol. **5**:363, 1920.

1a. Krause: Johns Hopkins Hosp. Bull. **22**:250, 1911.

that such maternal transmission occurs, but is always more or less irregular and inconstant, and the amount of immunity decreases with age and weight of the animal; the "inheritance" is probably always one of antibodies. Finally, if the predisposition is merely a non-specific condition of lowered resistance, it flies in the face of daily experience. Such patients react to other infections just as those normally constituted, and often exhibit marked physical and mental vigor. The stigmata of the tuberculosis candidate can be explained more rationally by regarding them as interferences with growth due to an accomplished infection rather than as earmarks of an inherited constitutional inferiority predisposing to a later infection. (*c*) Probably the most widely accepted notion is that the child of a consumptive family inherits neither the disease itself, nor any peculiar tendency to it, but merely an increased exposure to infection. There is little doubt that this is the effective factor in many cases. (*d*) There is, however, one other possibility, which forms the topic of the present discussion, viz., that the child inherits the disease not in a mendelian sense, but in the sense that constitutional syphilis is inherited; that is, it is infected during intrauterine life. Such infection, in the case of syphilis, we regard as a universal law, in tuberculosis we regard it as rare. Whatever disparity exists (and the disparity, we are inclined to believe, is not so great as is generally thought to be the case), may be explained as being due to the markedly greater invasive tendency of syphilis.

These several explanations of the origin of familial tuberculosis are discussed at greater length, but in the same general tenor, by Sitzenfrey [2] and by Péhu and Chalier.[3]

We are not concerned, in this paper, with minutiae of pathologic anatomy and histogenesis, but only with the epidemiologic, or, as Warthin and Cowie [4] so aptly express it, the sociologic and eugenic significance of prenatal tuberculosis. The cases are now so many that a detailed enumeration of them has become, in a sense, of as little practical importance as such an enumeration of appendicitis cases would be. We have been content to collect without distinction as to source, the cases listed in the bibliographies of Warthin and Cowie,[4] Sitzenfrey,[2] Péhu and Chalier,[5] Lanz,[6] Weber [7] and Chomé,[8] care being taken to eliminate duplicates. The distinction drawn by all previous writers between authentic and non-authentic cases, we have adhered to as

2. Sitzenfrey: Die Lehre von der kongenitaler Tuberkulose, etc., Berlin, 1909.
3. Péhu et Chalier: Arch. d. Méd. d. enf. **18**:1, 1915.
4. Warthin and Cowie: J. Infect. Dis. **1**:140, 1904.
5. Péhu et Chalier: Arch. d. méd. d. enf. **11**:1, 100, 1908; **17**:921, 1914.
6. Lanz: Arch. f. Gynäk. **104**:214, 1915.
7. Weber: Brit. J. Child. Dis. **13**:321, 359, 1916.
8. Chomé: Arch. mens. d'obstr. et de gynéc, Paris **7**:294, 1918.

closely as possible, in view of the fact that, naturally enough, there is no general agreement as to certain of the cases. The four or five cases listed by Warthin and Cowie in the doubtful class, as "probable" or "very probable" we have placed in the list of cases accepted as genuine (where, indeed, they are also listed by others), in the conviction that a truer notion of the actual situation is thus gained. To the total thus obtained we add with greater detail the small number we have found, not included in any of the lists above mentioned, and our own case.

LIST OF PUBLISHED CASES OF PRENATAL TUBERCULOSIS

	Authentic	Doubtful
Congenital tuberculosis of fetus and placenta	38	509
Tubercle bacilli but no histologic changes:		
Fetus and placenta	21	10
Fetus only	3	...
Same in fetus with histologic tubercle in placenta	4	...
Tuberculosis of placenta, with bacilli and histologic tubercle	44	...
Bacilli but no histologic tubercle, placenta only	3	...
Total	113	519

To this total of 113 authentic and 519 more or less doubtful cases of prenatal tuberculosis we have been able to add a number of cases.

Leuenberger [9] reports two cases. In the first, the mother suffering from an old tuberculosis of the kidney, ureter and bladder died of acute miliary tuberculosis and tuberculous meningitis in the eighth or ninth month of pregnancy. The placenta showed no macroscopic evidence of tuberculosis, but in sections there were found many typical tubercles, uniform in size and smaller than those in the maternal organs. Tubercle bacilli were found by direct examination in the capillaries of the fetal liver, but there were no histologic tubercles. Guinea-pig inoculation tests of the fetal blood and liver gave positive results. In the second case, the mother died of cavernous consumption following spontaneous abortion. Bacilli but no histologic tubercles were found in the fetal liver. Guinea-pig tests of the fetal blood were positive; of the fetal liver, negative. The placenta likewise contained no histologic tubercles, but bacilli were found in the intervillous spaces, especially at the edges of the white infarcts. A very few bacilli could be traced through the wall into the capillaries of the villi.

Sugai and Monobe,[10] using direct search in sections, found tubercle bacilli in three out of seven placentas from tuberculous mothers. (By the same method they found leprosy bacilli in all of twelve placentas from leprous mothers).

9. Leuenberger: Beitr. z. Geburtsh. u. Gynäk. **15**:456, 1910.
10. Sugai and Monobe: Zentralbl. f. Bakteriol. Orig. **67**:232, 1912.

Chomé [6] reports the case of a mother who died of chronic pulmonary tuberculosis twenty-four hours after delivery at term. The infant had no contact with the mother after birth, and was placed at once in a tuberculosis-free environment. The child was sick from birth, coughed on the seventh day, and when seven weeks old, enormous numbers of tubercle bacilli were found in the stools. At eight weeks it weighed less than at birth. There were râles in the lungs, and inoculation of guinea-pigs with material from feces gave a positive result in six weeks. The intradermal tuberculin test was negative. The child died at three months. At the necropsy there was found miliary tuberculosis of the lungs, with croupous pneumonia in the stage of red hepatization. The peribronchial and mesenteric lymph nodes were large and caseous. The middle ear on both sides contained pus and tubercle bacilli. The miliary tubercles in the lungs contained incredible numbers of tubercle bacilli. The liver contained early miliary tubercles with giant cells and a few bacilli. The spleen was packed with tubercles. The suprarenal medulla was caseous and contained many bacilli. The placenta was not examined. Chomé thinks that intrapartum infection in this case is excluded by the fact that the amnion ruptured only at the moment when the head disengaged. He suggests, as we do, that the lung may be a favorable culture medium for the tubercle bacillus because of the abundance of atmospheric oxygen and blood.

In addition to the above we have found the following titles to which we have not been able to get access: Királyfi's [11] article on congenital tuberculosis has a Magyar text which we cannot read, nor have we been able to find anyone who can translate it for us. Ludwig's [12] article on tuberculosis of the placenta and congenital tuberculosis, and Kerscher's [13] monograph we have not been able to obtain. Kerscher's monograph is the only one whose title gives promise of adding more material.

Our case adds one more clear instance of transplacental infection. The following is a brief abstract from the protocol of the necropsy, which was performed Oct. 24, 1919, by Prof. E. R. Mugrage, to whom we here express our grateful appreciation.

REPORT OF CASE

The body is that of a still-born Mexican female infant, stated to be in the ninth month of gestation. (The record in the University Dispensary shows a nine months' pregnancy.) The body is 45 cm. long and weighs 3,402 gm. Body heat is still present. There are several scars, oval in shape and somewhat depressed, varying in size from a pinhead to 5 cm. in diameter, scattered

11. Királyfi: Orvosi hetil. **49**:568, 1905.
12. Ludwig: Gynäckol. Helvet. **14**:25, 1914.
13. Kerscher: Kasuistischer Beitr., etc., Stuttgart, 1909-1910.

over the anterior aspect of both shoulders, and on the left cheek. The pleural cavities show widespread, firm, bandlike adhesions. The lungs sink in water and are studded with innumerable calcareous nodules. The kidneys are thickly set with small, grayish white nodules uniformly distributed throughout the cortex and medulla. The adrenals are much enlarged and the medulla filled with a large amount of caseous material. Macroscopic lesions are also present in the left ovary, both lateral ventricles, and in the anterior part of the thalamus. The other organs do not contain lesions visible to the naked eye. The fragments of the placenta, which were saved, contain numerous caseous nodules measuring 4 or 5 mm. in diameter.

Microscopic Examination.—(The structure of the tubercles in the lungs only is described. The lesions in the other organs are essentially identical.) The lungs are thickly set with tubercles varying greatly in size and stage of development. The earlier lesions consist of collections of epithelioid cells, which are large and circular at the center of the tubercle, becoming more and more flattened toward the periphery, until at the edge they are long and spindle shaped. Giant cells are rare but occasionally are found. Lymphocytes form a zone about the periphery, and some tubercles are completely infiltrated by small round cells. About the tubercles the air cells are filled with hyaline coagulated exudate, with a considerable number of polymorphonuclear cells. The larger tubercles are caseous at their centers. Many calcareous nodules are also present, probably representing a still later phase of the process.

The spleen and pancreas contain numerous calcified tubercles, and the suprarenal and ovary contain caseous tubercles. The kidney contains many tubercles, frequently caseous. After prolonged search through many sections, a few tubercle bacilli were found in the kidney lesions. They could not be demonstrated in any other organ. The liver is markedly fatty and contains an occasional small tubercle. The floor of the lateral ventricle contains an occasional caseous tubercle. The placenta shows numerous necrotic areas and tubercles with caseous centers.

It is to be regretted that no animal inoculation tests could be made owing to the tissue being fixed prematurely; but the diagnosis is firmly established by the character of the histologic changes, and the finding of tubercle bacilli in the kidney. The fact of still-birth at term precludes intrapartum infection.

History of the Mother.—Mexican, 36 years old, has had five children, four of whom died of influenza in 1918. Denies miscarriages. The examination made at the dispensary previous to confinement revealed no active tuberculosis but one made at the time of delivery by Dr. H. O. Calhoun (to whom we express our sincere thanks) revealed an area of dulness with râles at the right apex. Thirteen months later (November, 1920) she is apparently healthy and well nourished but still has a dull area with râles as before. She raises little or no sputum.

In view of all the difficulties which, except in rare cases, attend the search for tuberculosis in fetus and placenta, and the fact that they are rarely subjected to exhaustive examination unless there is some special reason therefor, this collection of cases is by mere weight of numbers an imposing one; imposing enough to lift prenatal tuberculosis out of the class of medical curiosities and to stimulate consideration of the broader aspects of the question. But if, as is maintained by many, prenatal tuberculosis is inevitably fatal within a few weeks or months after birth, the condition becomes again merely an interesting phenome-

non of little practical importance. The question of its significance in human pathology is intimately bound up with the question as to the validity of the old Baumgarten theory of latency. By the very nature of the case, the theory is hardly susceptible of objective proof or disproof, and can only be approached indirectly. We shall review as briefly as possible the arguments which Baumgarten himself has made familiar, and submit certain further considerations which seem to us not devoid of weight.

The possible common portals of entry are (a) the respiratory tract, by the inspiration of bacilli suspended in dry dust, or, still wet, in droplets of saliva and mucus, coughed, sneezed or otherwise expelled from the mouths and noses of consumptive persons; (b) the digestive tract, by swallowing bacilli reaching the mouth as above, or in food and drink; (c) the tonsils, similarly. Baumgarten [13a] has argued that in the first place, the real or apparent primary localization of the disease in the lungs is absolutely no proof of an aerogenic origin. The relative frequency of pulmonary tuberculosis, as compared to other localizations, is due merely to a special predilection of the organism for the lungs. The extraordinarily tortuous character of the path to be traveled along the bronchi, the defense against entrance afforded by mucin and cilia, and the very slow progress into the lung of any given unit of air, probably render the bronchial tree the most difficult of the routes into the lung. Animals are rarely infected by breathing bacillus laden dust, perhaps due to attenuation caused by drying. Breathing moist bacilli in spray produces a higher percentage of infections; usually caseous pneumonia or bronchopneumonia, rarely bronchiolitis or perbronchiolitis. But the same processes can be produced in typical form by hematogenous infection. On the whole, the droplet method of infection, Baumgarten thinks, has more in its favor that the dry dust method, but this is far from proving that the former is the most common mode of infection under normal conditions.

Feeding experiments are much more successful, especially when the bacillus is administered in small doses over a long period, thus simulating as closely as possible the natural conditions of infection, rather than in only one or two large doses. Moreover, calves, which never become infected by breathing infected dust, etc., do so regularly in the feeding experiment. Necropsies on such animals, performed at successive stages of the process, prove that the (bovine) bacillus may pass the intestinal wall without producing any local lesion, and can be found in the mesenteric glands, even when these are not enlarged. Later the bacilli reach the thoracic organs, usually only the peribron-

13a. Baumgarten: Samml. klin. Vortr., No. 281, 1882; (Inn. Med., No. 74, p. 1955); Deutsch. med. Wchnschr. **35**:1729, 1909.

chial glands, but sometimes the lungs also. Since no direct path from the mesenteric to the bronchial glands exists, the transfer must be assumed to take place via the thoracic duct or portal vein.

Baumgarten insists that these facts can not be transferred unhesitatingly to human pathology. Primary tuberculosis of the mesenteric glands is rare in man, and a primary lesion due to the bovine type is rarer still. Even when the bovine type does reach the glands it grows but meagerly and soon dies out. It is rarely found in other lesions, especially the lungs, and he does not believe that an infection due to the bovine type could lose this character by conversion of the bacillus into the human type, since this would require passage of the strain involved through several human hosts. Human tissue, on the other hand, is a favorable medium for the human type of bacillus, so that these objections do not apply to infection with the latter. In the vast majority of cases of combined pulmonary and intestinal tuberculosis the pulmonary lesion is obviously the older. But just as this fact does not prove aerogenic origin, so involvement of the intestines, even if very common, would not prove that the intestine serves as a frequent portal of entry. If that were the case, the bacillus must be assumed to have passed the intestinal wall and mesenteric glands without injuring them, and this, he insists, the human type, in contrast to the bovine type, does not do.

Baumgarten's argument, however, is open to criticism. His thesis requires that, while postnatal infection through the intestinal tract is looked upon as unable to reach the lung without leaving indications of its passage along the route followed, prenatal infection through the placenta and umbilical vein shall be assumed to be able to do just that. Schmorl and Kockel [14] long ago showed that the bacillus is found more abundantly in the fetal liver than anywhere else in prenatal tuberculosis, and often unaccompanied by histologic changes. Conceivably this might be due to infection having occurred so short a time before the examination was made that no opportunity was afforded for the customary changes to develop. Be this as it may, there is no question that lesions in the liver, other than those obviously arising in the last days or weeks of life, are very rare in pulmonary tuberculosis. Baumgarten's argument on this point therefore cuts both ways.

To the above brief and very incomplete sketch of Baumgarten's argument in favor of latent and prenatal infection we would add the following considerations:

1. There is a general tendency to apply to man the ideas of von Behring [15] regarding the age period of infection in cattle. Quite

14. Schmorl and Kockel: Beitr. z. path. Anat. u. z. allg. Path. **16**:313, 1894.
15. Von Behring: Deutsch. med. Wchnschr. **29**:689, 1903; **30**:193, 1904 abstr. Zentralbl. f. Bakteriol. Refer. **34**:136, 729, 1903.

recently, for example, von Jaksch [16] has complained with some petulance of a failure in certain quarters to apprehend the "fact" that the human animal is insusceptible to tuberculous infection (aside from such purely local manifestations as the anatomist's tubercle) after the age of six years. Griffith [17] puts it somewhat differently when he defines tuberculosis as a disease of childhood. But if we accept the theory that tuberculous infection, either always, or only usually, occurs either before birth, or during the years of infancy and childhood, we cannot escape accepting "in principle," as the diplomats say, the theory of latency; because in the vast majority of cases, manifest symptoms develop only later in life, sometimes very late, and often in connection with some special tax on the vitality, such as measles, whooping cough, pneumonia, pregnancy, etc. Moreover, if an infection acquired during the first weeks or months after birth may remain latent for years, it is hard to see any valid reason why an infection acquired during the last weeks or months before birth should not behave in the same way. Certainly, the struggle for existence is not more difficult or exhausting for the child in utero than for the child not thus protected.

2. The mechanism of latency may be placed on a more solid theoretic basis than that provided by Baumgarten's theory that the bacillus preserves and prolongs its individual life by "slumbering" over long periods. It has been abundantly proved that immune bodies present in the mothers' blood may find their way into the fetal circulation (Coca,[1] Krause [1a] and others). Since these are isoimmune bodies, and therefore practically identical with any immune bodies which might be produced by the fetus itself, they would tend to be only very slowly eliminated, and would no doubt protect the child as completely, and over as long a period as an active immunity of equal titre. A partial immunity would tend to prevent active progress of the disease, without, however, being able to destroy the bacillus completely, thus creating a situation analogous to that which we assume to exist, in order to account for the progressively narrowing field of activity ordinarily observed in the later stages of syphilis. Sitzenfrey noticed that the extent of the disease in fetal tuberculosis is roughly directly proportional to the extent and activity in the mother. This is probably usually true, though the cases of Warthin and Cowie, Grulee and Harms,[19] and our case prove that it is not necessarily true. The same rule stated differently may be useful here. Let us put it in this way: the extent and severity of the disease in the fetus is, roughly, inversely proportional to the mother's immunity.

16. Von Jaksch: Zentralbl. f. Inn. Med. **39**:545, 1918.
17. Griffith: New York M. J. **109**:485, 1919.
19. Grulee and Harms: Am. J. Dis. Child. **9**:322 (April) 1915.

3. Numerous researches of recent years prove conclusively that what we term latency is often not latency at all, but defective diagnosis; or more often, no diagnosis at all. We shall mention only a few of the many works in this field. Landouzy [20] reports in detail seven cases of infantile tuberculosis, with necropsy findings, in children varying in age from 6 weeks to 12 months. These occurred in a total of twenty-three deaths, or 30.4 per cent., in a hospital population of 127 children, in a period of 4 months. In another series [21] he reports twenty deaths, fifteen with necropsy, three without necropsy, and two doubtful, in children varying in age from 3 to 24 months. Total deaths for the period were sixty-nine, including eleven incidental to a severe epidemic of diphtheria. The fifteen deaths with necropsy constitute 20.7 per cent of the total, and the largest single item in the list of causes of death. Landouzy, who is a firm believer in the Baumgarten theory of latency, contends very earnestly that tuberculosis, instead of being rare in childhood, "as commonly supposed," is the most important cause of infantile mortality. Klare,[22] in a clinical lecture on tuberculosis in childhood, maintains that practically every one becomes infected by the fourteenth year of life. Griffith [17] collected data showing that, when the diagnosis is based on sensitization tests, tuberculosis is rare in the first three months of life, but increases rapidly up to as high as 83 per cent. of the children examined, at 14 years of age. Under the more rigid criterion of necropsy, the percentage is naturally somewhat lower, viz., 40 per cent. in 848 necropsies at Vienna, 35 per cent. in 332 necropsies at Philadelphia, 38 per cent. in 1,675 necropsies at Paris, distributed as follows:

	Per Cent.
Up to age of 3 months	1.82
From 3 to 6 months	18.0
From 6 to 12 months	26.0
From 1 to 2 years	40.0
From 2 to 5 years	60.0
From 5 to 10 years	67.0
From 10 to 15 years	71.0

It is to be noted that the failure to find visible tuberculosis in early infancy does not at all prove that the infection had not already taken place, as is shown by the large number of cases in the table given earlier, of infection without histologic changes. Honl,[23] who gave this condition the name, status bacillaris, suggested that it might be due to retardation of growth of the bacillus, through lack of free

20. Landouzy: Rev. de méd. **7**:383, 1887.
21. Landouzy: Rev. de méd. **11**:721, 1891.
22. Klare: Aertzl. Rundschau **28**:67, 73, 1918.
23. Honl: Bull. intern. de l'Acad. de Sc. de l'Empereur Francis Joseph I, 1894 (cited from Warthin and Cowie).

oxygen. Spolverini [24] studied a series of 900 children, varying in age from 3 to 12 months. Marantic and undergrown children, and children ill with, or recently recovered from, other diseases were not included in the series. The children were first tested by the percutaneous tuberculin method and if this was positive, were examined radioscopically and by the other recognized methods of physical diagnosis. Some children negative on the first test became positive when tested again several months later. In almost every case, when one child of a family gave positive results, other children in the family were also found to be positive. Of the 900 children examined, sixty-three, or seven per cent., were found to be tuberculous. Of the sixty-three positive cases, eight children were from 3 to 4 months old, twenty-two from 4 to 6 months, and thirty-three from 6 to 12 months. He thinks that his results are too low because several of the children were undersized, and probably failed to react because of general ill health.

The term, latency, is usually taken as covering all that period in the progress of the disease from its actual inception to the onset of manifest disturbance of health. The above figures would indicate that this period would be materially shortened, and perhaps reduced to something like a rational period of incubation, if every child, regardless of the apparent state of its health, could enjoy the benefit of an exhaustive search for the disease, by the aid of the most refined diagnostic methods. Latency as a problem might then disappear.

4. It seems to us also that not enough account is taken of possible variations in the virulence of the bacillus. In one of Schrumpf's [25] cases the bacillus recovered from the placenta and fetal tissues was so avirulent that it failed to kill a guinea-pig. The case of Repaci,[26] of a child dying on the twenty-ninth day of life, is doubted by Weber simply because the child lived so long. For the same reason Weber doubts the authenticity of Hamburger's [27] case, in which the child lived nearly eight weeks. But everyone who has employed animal tests for the diagnosis of tuberculosis in adults knows that the animals sometimes live an exasperatingly (when one is waiting to make the diagnosis) long time. Certainly slow progress of the disease is no reason for doubts as to its nature.

Whatever the facts may ultimately prove to be, there is already sound reason for believing that prenatal infection is an important, if not the most important, method of propagating the disease. Nor is

24. Spolverini: Riv. de clin. Pediat. **17**:169, 1919; also Tuberculosi **10**:239, 1918.

25. Schrumpf: Beitr. z. path. Anat. u. z. allg. Path. **42**:225, 1907.

26. Repaci: Osp. d. Bamb. d. Milan **1**:147, 1913 (abstr. Brit. J. Child. Dis. **10**:547, 1913; cited from Weber).

27. Hamburger: Beitr. z. Klin. d. Tuberk. **5**:197, 1906 (cited from Weber).

the mother the only possible source of danger. In the case of the father, animal experimentation and for man statistical studies constitute almost our only weapons for attacking the problem. Friedmann's [28] experiments are classical. He found that when buck rabbits are injected in one or both vasa deferentia with either the human or bovine type of bacilli and mated a few weeks later with healthy females, tubercle bacilli could usually be demonstrated in the seven day embryos. If the injection was made into the testis instead of the vas, the bacilli could likewise be found in the seven day embryos, provided that not too long a time elapsed between the injection and mating. When the interval was too long (four weeks or more) conception did not take place. If the injection was made intravenously, the bacilli could sometimes be found in the six day old embryos. When the interval between injection and mating was four weeks or more, the bacilli were found less readily but could still be demonstrated in a few instances. When the difficulties of the search, a veritable hunting for a needle in a haystack, are taken into account, these positive results become very significant.

Friedmann also analyzed 983 cases of pulmonary tuberculosis with hereditary taint from the records of the second medical clinic of the University of Berlin. Among the 983 cases were 503, or 51.2 per cent., with a history of tuberculosis on the father's side, 323 cases, or 32.8 per cent., with a similar history on the mother's side, and 157 cases, or 15.9 per cent., with such a history on both sides. He quotes the paper of Klebs [29] who found that in a family with a history extending back to the middle of the eighteenth century, many of whose members he had himself known, consumptive males married to healthy females often got consumptive children. Several times he observed that one and the same woman bore consumptive children when married to a consumptive husband, and later, with a healthy husband, bore healthy children. Forty per cent. of the children of consumptive mothers and only 4 per cent. of those of consumptive fathers were healthy, so that tuberculosis in the father is ten times as dangerous for the child as tuberculosis in the mother. Such data are difficult to harmonize with the view that tuberculosis is always or generally contracted after birth, that it recurs in families simply because of greater exposure, or that on the other hand, it is due to any sort of predisposition.

Finally, Friedmann cites from the literature two cases of "proved" congenital tuberculosis derived from the father. Sarwey [30] reported

28. Friedmann: Virchows Arch. f. path. Anat. **181**:150, 1905.
29. Klebs: München. med. Wchnschr. **48**:129, 1901 (cited from Friedmann).
30. Sarwey: Arch. f. Gynäk. **43**:162, 1892; abstr. Schmidt's Jahrb. **240**: 174, 1893.

a case (included in Warthin and Cowie's list as "very doubtful") from Baumgarten's laboratory, of a still-born hemicephalic monster, with missed labor, carried over eleven months, in which there was a tuberculous abscess of the cervical vertebrae. The father had suffered for a long time with cough and a tough expectoration, and the paternal grandfather had died of chronic pulmonary tuberculosis. There was no demonstrable tuberculosis in the mother. Landouzy described the case of a child who died when 24 hours old of tuberculosis. The father was a consumptive and the mother quite healthy. Landouzy [31] reports the following two family histories, which could, he thinks, be duplicated from the experience of any active practitioner. An officer fell sick in 1878, in the midst of apparent sound health, with tuberculosis, which progressed with various complications to his death in 1888. He was married in 1876 to a "superb young girl," 21 years old. He had five children; the first, a boy, born at term in 1876, developed normally and died at eight months of cholera infantum. The second, a girl, born before term (seventh or eighth month) in 1878, died twenty-four hours later in convulsions. This is the case, so far as we can make out, cited by Friedmann as a proved case of paternal transmission. Comment seems superfluous. The third child, born at term in March, 1881, was brought up like the first under the best possible conditions. It died when 6 months old with classical symptoms of tuberculous meningitis. The fourth, a girl, born at term in February, 1882, also died when 6 months old with symptoms of tuberculous meningitis. The fifth, a boy, born at term in 1883, was breast fed and brought up far from the father, in the open country. At 5 months, he fell sick with a purulent otitis media, which ultimately extended to the meninges and was diagnosed by a physician, the uncle of the child, as tuberculous. The mother remains perfectly well fifteen years later, in spite of five pregnancies in seven years and the sorrows and trials of her married life. It will be agreed, he says, that if these children died of tuberculosis, they received the disease from the father, not from the mother. In another family, four children, all brought up carefully and fed exclusively on breast milk, partly from the healthy mother, partly from a healthy nurse, died of tuberculosis at ages ranging from 3 to 12 months. The father, who had no genito-urinary tuberculosis, had a pulmonary process in the first or second stage. He coughed but raised no sputum. Moreover three of the children lived removed from the father from birth. Landouzy mentions an experiment of his own, similar to one of Friedmann's, in which six out of sixteen male guinea-pigs, inoculated with tubercle bacilli, begot tuberculous offspring.

31. Landouzy: Rev. de méd. **11**:411, 1891.

The importance of this matter lies in this, that to the extent that the conclusions outlined are sound, all our present day methods of attacking tuberculosis are merely palliative, designed to prolong the life of the consumptive, but having not the slightest effect on the source of contagion. A year ago one of us (R. C. W.) heard Dr. V. C. Vaughan say, in the course of an impromptu after-dinner talk to a gathering of physicians that thirty years ago he had been wont to prophesy, with the enthusiasm of unbounded faith, "No tuberculosis by 1920." Some contemporaries, less sanguine than himself, thought 1950 a safer estimate. "Now," said Dr. Vaughan, "the years have brought disillusionment and I feel that we shall be lucky if we stamp out tuberculosis in five hundred years." We would not be too pessimistic, but we believe that five times five hundred years may well find us just about where we are today, with a falling death rate, due to an increasing proportion of cures and greater prolongation of life of the consumptive, but with no very great reduction in the morbidity rate, unless indeed we change our methods. It will seem harsh and heartless to many to argue that although it may well be doubted whether if leprosy had been allowed to spread unchecked, it would ever have wrought anything like the havoc caused by tuberculosis,[32] yet general fear and the tradition of centuries sanction a degree of harshness in the control of leprosy, which we would not dream of employing toward the consumptive. It is worth considering whether our methods of control in tuberculosis are not in large measure determined by what we like to call sentiments of compassion, but which really deserve a much harsher name. It could be argued with a good show of reason that methods of control based on education, rather than segregation, constitute a cowardly repudiation of the rights of unborn, uncounted millions.

CONCLUSIONS

1. Prenatal tuberculosis has ceased to be a mere curiosity of the laboratory, and has become a pressing problem of the sanitarian.

2. The facts at hand are significant enough to command the active employment of every agency by which further facts may be elicited.

3. To the extent that the spread of the disease is due to prenatal, rather than postnatal, infection, present methods of control must be revised and amended, even at the expense of those sentiments of compassion and tolerant forbearance by which our present efforts are so notably handicapped.

32. II Kings, v. 1 et seq. "Now Naaman, captain of the host of the king of Syria, was a great man with his master, and honorable, because by him the Lord had given deliverance unto Syria: he was also a mighty man in valor; but he was a leper," etc. Certainly, the picture of this warrior and national hero, living en famille with wife and servants, hardly suggests that leprosy inspired the horror three thousand years ago that it does today.

A CONVENIENT ELECTRODE FOR EXPERIMENTAL ELECTROCARDIOGRAPHIC WORK*

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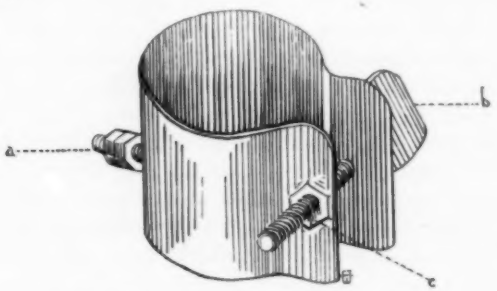
In undertaking a series of experimental electrocardiographic studies, we found a large number of animals that were not suitable for our work. But before the adaptability of an animal could be determined with the usual experimental electrocardiographic electrode, it was necessary to anesthetize it and make an incision in the skin in order properly to insert the electrodes. This procedure requires considerable time and sometimes results in an infected wound if the animal is not used at once.



(*a*) Attachment for lead wire.
(*b*) Long screw for adjusting diameter of electrode.
(*c*) Nut for screw *b*. It is not necessary to have a nut on each side of the adjustment leads.

To obviate this difficulty we have adopted a very convenient type of electrode, consisting of an adjustable copper plate with an attachment for the lead wires. The width of the cuff is 1¾ inches, and the minimum diameter, after it has been bent roughly to conform to the shape of the leg, is 1 inch. The copper is flexible, and is readily adjusted to a large or small animal by means of a thumbscrew.

The connection of the lead wire to the copper plate is secured by soldering a copper rivet to the outside of the electrode. Care is taken to place the solder only around the edge of the rivet; otherwise it would interfere with conduction. The rivet is then threaded and provided with lugs to hold the lead wire.

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*From the Division of Experimental Surgery and Pathology, Mayo Foundation.

In using this electrode the animal's leg is shaved and the copper cuff snugly adjusted by means of the thumbscrew. No especial attention is given to the cleansing of the skin, although excess dirt should always be removed.

We have found the instrument to be very adaptable in making studies on unanesthetized animals. In a large series of experiments we have not had more than 1,000 ohms resistance, and in all respects this electrode has been an improvement over the type generally used in experimental electrocardiographic work.

BOOK REVIEW

THE HEART AND THE AORTA: STUDIES IN CLINICAL PATHOLOGY. By H. Vaquez, Profeseur agrégé à la Faculté de Médecine de Paris, Médecin de l'Hôspital San-Antoine; and E. Bordet, Chef de laboratoire Adjoint à la Faculté de Médecine de Paris. Translated from the Second French Edition by James A. Honeij, M.D., and John Macy, M.A. Pp. 256. 181 illustrations. Yale University Press, New Haven, Conn.

In this book the authors begin with a description and comparison of the various radiographic methods of examining the heart and the aorta, including their personal technic. They consider that there are three reliable methods, teleradiography, orthodiography and teleradioscopy. The latter two furnish identical information and are designated as radioscopy of percision. They point out that teleradiography and radioscopy of percision each have its advantages and that the association of the two methods gives nearly perfect results. If, however, only one is to be used the orthodiographic examination gives more precise information.

In the following chapter the authors describe the normal cardiac shadow in the frontal and oblique positions and consider variations in the physiological form of the heart. In subsequent chapters changes produced in the cardiac shadow by various pathological conditions as chronic valvular diseases, congenital defects, affections of the pericardium, aortitis and aneurisms of the thoracic aorta are illustrated. The last chapter discusses the localization of war projectiles in the heart and pericardium. The points of the authors are well illustrated by diagrams.

This volume with its numerous illustrations demonstrates very clearly the importance of radiographic examination of the heart and aorta. The authors seem conservative in their claims and have apparently accomplished their purpose in compiling the work. It is fortunate that Dr. Honeij has translated it in English. It will further the employment of this valuable method of examination and should serve as a useful reference to the radiologist and the physician.